The Chemistry of Ynamide and Its Application in Organic Synthesis

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Abstract: Ynamide, is an understudied but attractive class of alkynes, activated by the donating ability of the nitrogen adjacent to alkynes. With the nucleophilicity on β-carbon and the electrophilicity on α-carbon of ynamides, this review summarizes the syntheses of ynamides and miscellaneous reactions - oxidation, rearrangement, cyclization, and cycloaddition to construct complicated heterocyclic rings. The synthetic methodologies were further applied into natural products synthesis, *e.g.* marinoquinolines A and C, aplidiopsamine A, rigidin A, and 7-azaserotonin derivative.

Keywords: ynamide, yndiamide, thioenamide, haloenamide, keteniminium, Witulski rearrangment, Ullmann coupling, dipolar cycloaddition, α-ketoimide, polycyclic alkaloids.

INTRODUCTION

The carbon-carbon triple bond is one of the most fundamental and valuable functional groups in the organic synthesis. A heteroatom substitution on the triple bond further enriches the reaction versatility. One useful substrate is ynamine, which contains a nitrogen atom directly connected to the triple bond. Conjugation of the nitrogen lone pair readily assists the electrophilic functionalization of the β-position of ynamines, and α-carbocation initiated nucleophilic addition or cyclization reactions (Scheme **1**). However, the synthetic utility of ynamines remained limited due to difficult preparation and handling. They are liable to hydrolyse to amides in an expensive manner. The ynamides were therefore tunable by introducing diversified amides, *i.e.*, amides, sulfonamides, carbamates, oxazolidinones, imidazolidinones, and lactams (Scheme **1**). Ynamides, with weakened electron-donating electron lone pair of the nitrogens towards the alkynyl motifs, have been found to be more stable and practicable than conventional ynamines.

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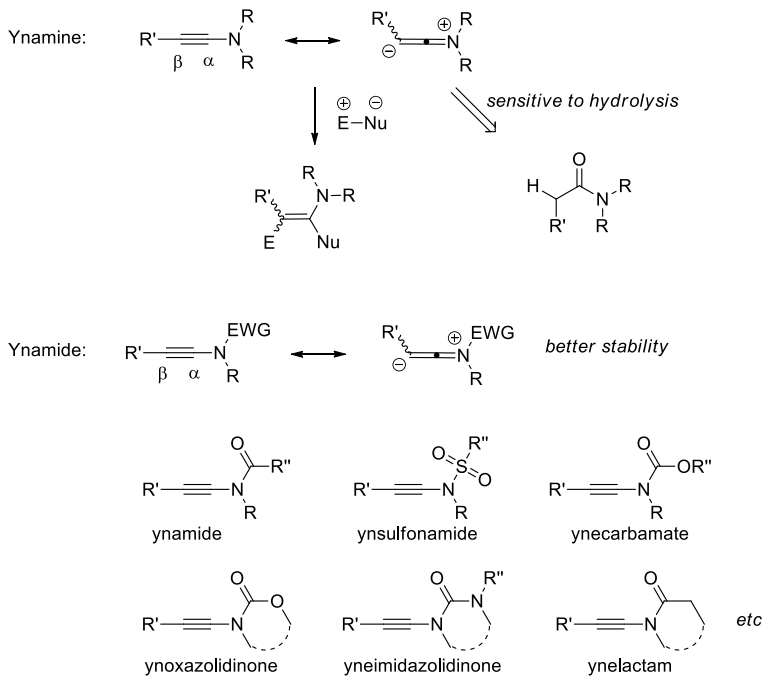


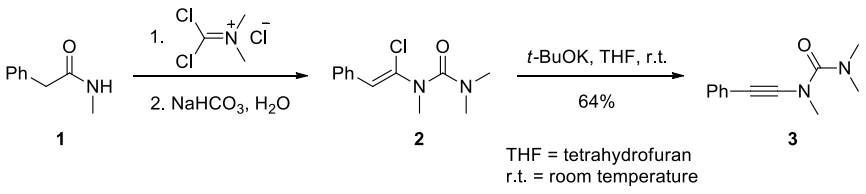
Scheme 1: General structures of ynamine and ynamide.

The ynamide chemistry, emerging several decades ago, has been gaining more and more attentions since 2000. Hsung's group [1, 2] and Evano's group [3, 4] have published elegant reviews to cover the development. This review focuses on recent developments of syntheses and applications of ynamides after 2010, in order to reveal the value of ynamide chemistry in organic synthesis.

PREPARATIONS OF YNAMIDES

Dehydrohalogenation

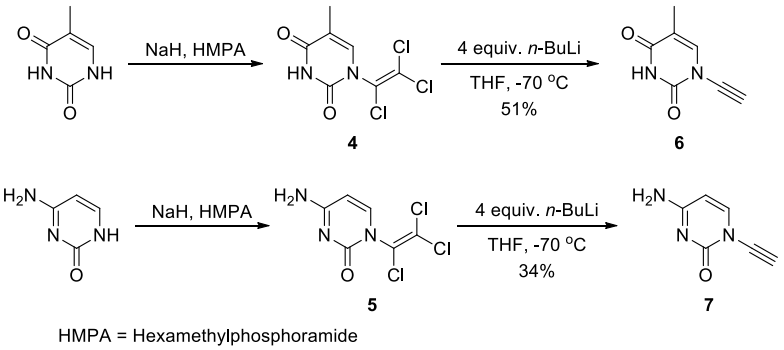
Dehydrohalogenation of halo-substituted enamides was the initial method of preparing ynamides. Viehe *et al* [5] reported the first case of preparing ynamides. *N*-(1-chloroalkenyl)urea **2**, generated from secondary acetamide **1** and phosgene immonium chloride, undergoes dehydrochlorination at room temperature with *t*-BuOK to afford *N*-alkynylurea **3** in moderate yield (Scheme **2**).



Scheme 2: The first case of synthesizing ynamide.

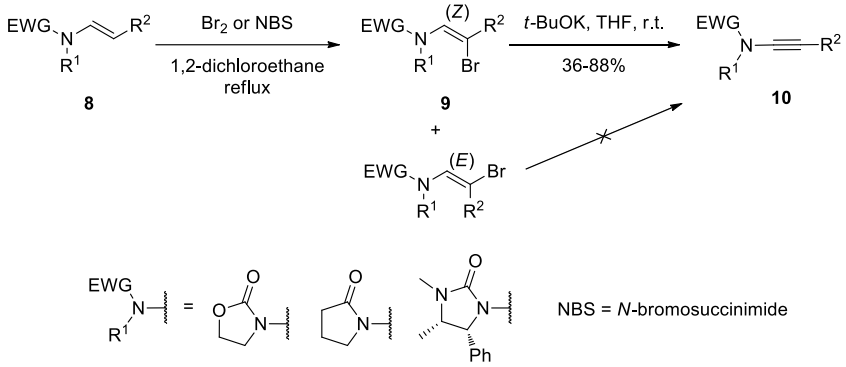
Another case is thymine / cytosine [6] derived chloroenamides **4** and **5**, obtained by nucleophilic additions of thumines / cytosines to tetrachloroethylene. Dechlorination

(lithium-chlorine exchange) of **4** and **5** with *n*-BuLi occurred smoothly at -70 °C to render ynamides **6** and **7** in 51% and 34% yields, respectively (Scheme **3**).



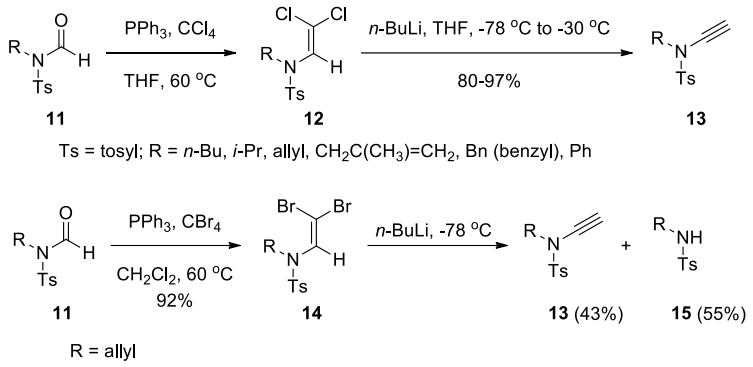
Scheme 3: Lithium-chlorine exchange of chloroenamides to ynamides.

Hsung and co-authors [7] furthered explored the substrate scope to β-bromoenamides, prepared by bromination of the corresponding enamides **8**. E2 elimination of hydrobromide from β-bromoenamides **9** with *t*-BuOK afforded ynamides **10** in 36~88% yields (Scheme **4**), under which conditions, pyrrolidinones, oxazolidinones and imidazolidinones were tolerated. However, transformation of *E*-isomers of **9** into ynamides failed.



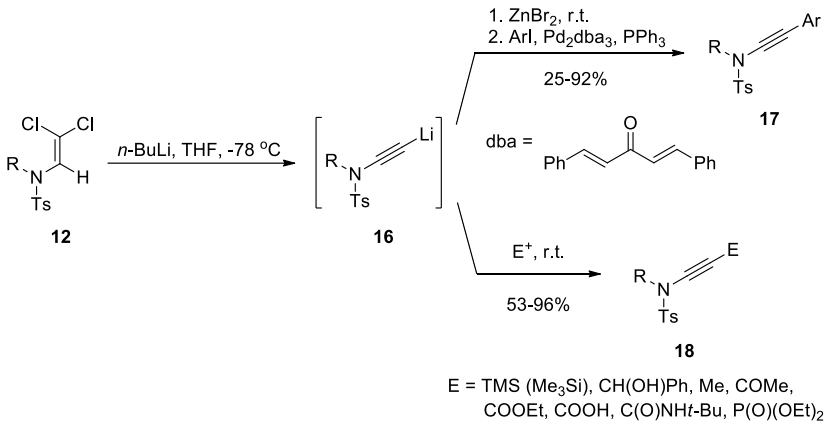
Scheme 4: Synthesis of ynamides from β-bromoenamides.

Brückner [8, 9] modified the substrates for ynamides *via* dehydrohalogenation. β,β-Dichloroenamides **12**, obtained by Corey-Fuchs reaction of *N*-formyl-tosylamides **11**, were converted to terminal ynamides **13** in satisfying yields according to lithium-halogen exchange (Scheme **5**). β,β-Dibromoenamides **14**, however, were not tolerated, resulting in a mixture of terminal tosylynamides **13** and tosylamides **15**.



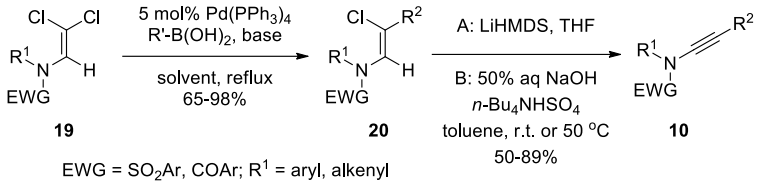
Scheme 5: Synthesis of ynamides from β,β-dihalogen enamides.

The lithiated ynamide intermediates **16**, obtained from the dechlorination of β,β-dichloroenamides **12** with 2 equivalents of *n*-BuLi, are useful for various transformations (Scheme **6**). Transmetalation with $ZnBr_2$ and Negishi coupling reactions with aryl iodides afforded aryl-substituted ynamides **17** in moderate to good yields, according to Saá's work [10, 11]. They also found that such lithiated ynamide intermediates could be trapped by diverse electrophiles [12] to render functionalized internal ynamides **18** in high yields. In the case of benzaldehyde as an electrophile, the yield was improved significantly than the direct functionalization of terminal ynamides.



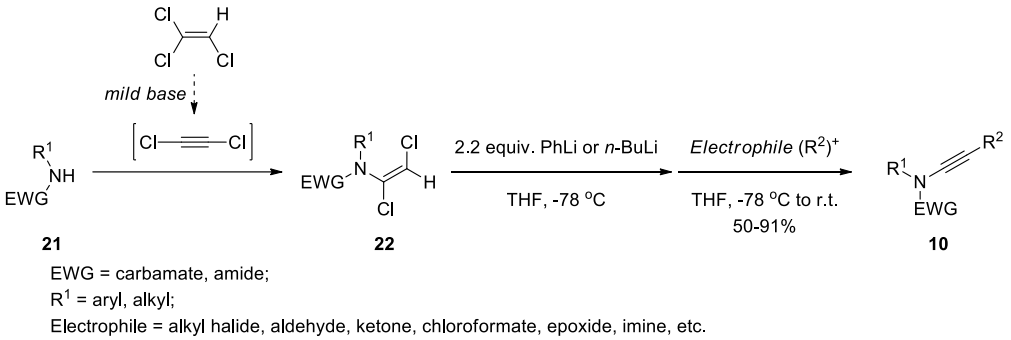
Scheme 6: Functionalization of terminal ynamides with dichloroenamides.

Cossy *et al* [13] also developed the functionalization of ynamides using Suzuki-Miyaura coupling reaction of β,β-dichloroenamides **19** as the key step (Scheme **7**). (*Z*)-β-chloroenamides **20**, which would not undergo a second-round Suzuki-Miyaura coupling reaction, finally delivered ynamides **10** in moderate to good yields, upon treatment with LiHMDS (lithium hexamethyldisilazide) [7].



Scheme 7: Synthesis of ynamides *via* Suzuki-Miyaura coupling of β,β-dichloroenamides.

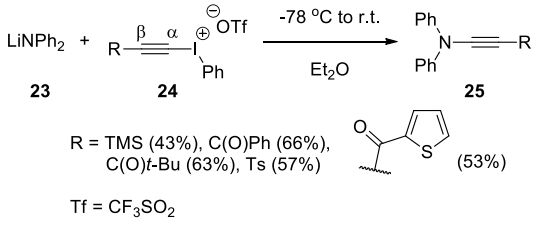
Reccently, Anderson *et al* [14] reported a modular synthesis of ynamide using TCE (trichloroethene) as an inexpensive two-carbon synthon. A wide range of amides and electrophiles can be converted to the corresponding ynamides in good yields (50~91%) (Scheme **8**), through lithium-chlorine exchange of α,β-dichloroenamides **22**. This method thus overcomes those limitations mentioned in the above approaches.



Scheme 8: Synthesis of ynamides from TCE-derived α,β-dichloroenamides.

Alkynyliodonium salts

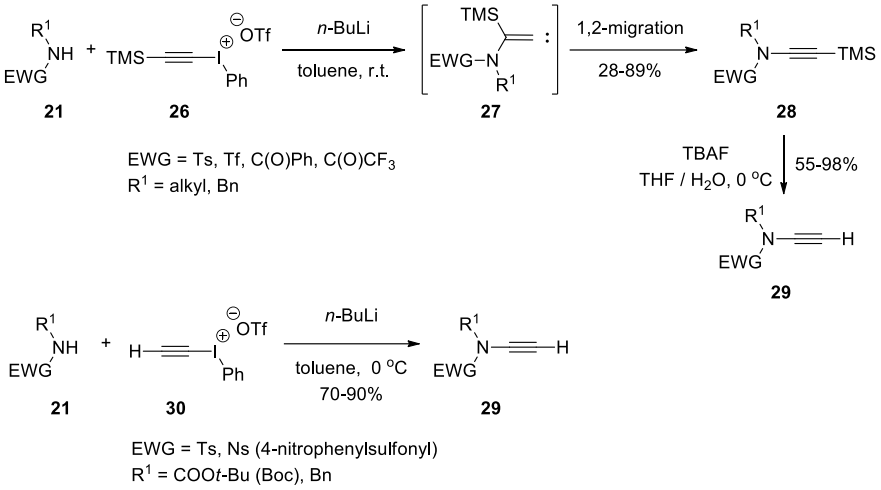
An alternative approach to ynamines / ynamides is to employ the highly electrophilic alkynyliodonium salts. In Stang's pioneering report [15, 16], the nucleophilic addition of lithium diphenylamine **23** to the β-position of alknyliodonium salts **24** delivered ynamines **25** in moderate yields, *via* 1,2-alkyl (or TMS) migration of vinylcarbene intermediate (Scheme **9**).



Scheme 9: Synthesis of ynamines from 1,2-alkyl migration of vinylcarbenes.

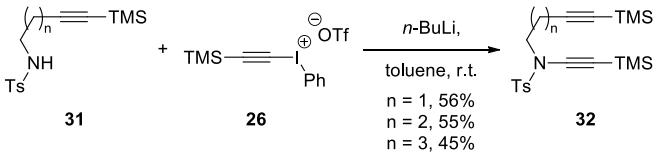
Witulski and co-authors [17, 18, 19] extended this protocol to access ynamides. Nucleophilic addition of lithiated amides to the readily prepared trimethylsilyl alkynyliodonium salts **26** produced the desired ynamides **28** *via* 1,2-migration of the silyl group to highly electrophilic vinyl carbene intermediates **27** (Scheme **10**).

Deprotection of TMS with TBAF (tetrabutylammonium fluoride) yielded the terminal ynamides **29** in good to excellent yields. Their later studies [20] demonstrated that the terminal ynamides **29** could also be synthesized from ethynyliodoniumtriflate **30** directly.



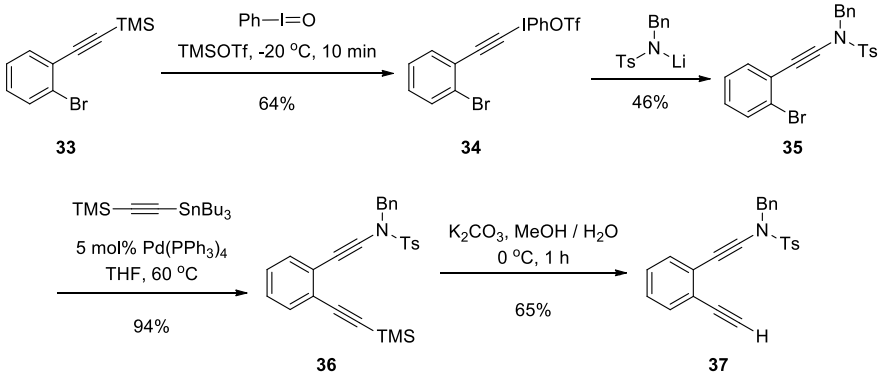
Scheme 10: Witulski's rearrangement to ynamides.

Rainer *et al* [21, 22] also used trimethylsilylethynyliodonium triflate **26** to prepare the desired yne-ynamides **32** (Scheme **11**).



Scheme 11: Synthesis of yne-ynamides.

A modified procedure of preparing alkynyliodonium salt was to replace $PdI(OAc)_2$ with PhIO (iodosobenzene) by König *et al* [23] (Scheme **12**).

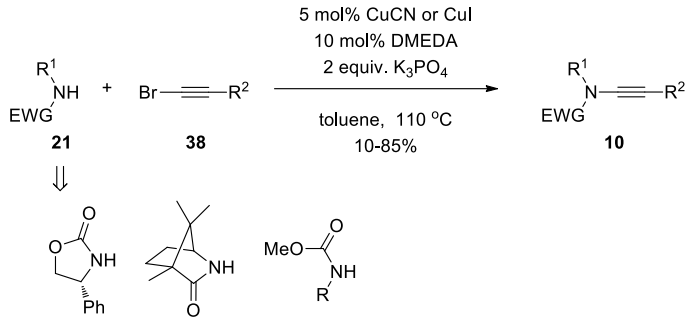


Scheme 12: Synthesis of yne-ynamides.

The above studies establish a valuable strategy for ynamide preparation. However, the alkynyliodonium salts are limited to silyl, aryl and electron-withdrawing substituents.

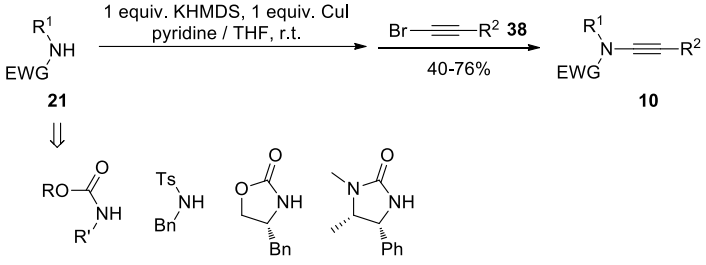
Ullmann coupling of amides

With the renaissance of copper catalysis, Hsung's group [24] made a breakthrough in ynamide synthesis in 2003 by developing a Cu(I)-catalyzed coupling reaction of alkynyl bromides **38** with amides **21**, including oxazolidinones, lactams, and carbamates, using DMEDA (*N,N'*-dimethylethylenediamine) as the ligand and K_3PO_4 as the base (Scheme **13**). Upon harsh heating, the ynamides were produced in low to moderate yields.



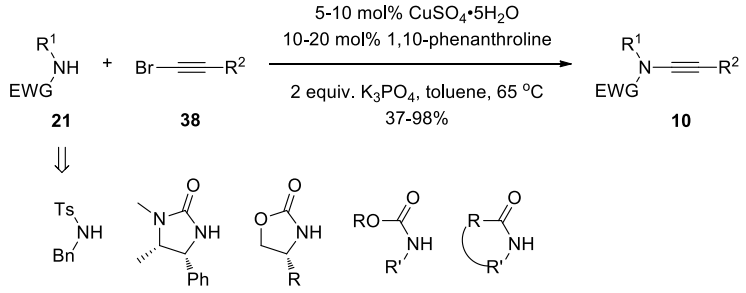
Scheme 13: First report of Ullmann coupling to ynamides.

Later in the same year, Danheiser's group [25] revised the sluggish Hsung's condition and achieved a mild Ullmann coupling by enhancing the nucleophilicity of amides. Deprotonation of amides **21** under KHMDS and subsequent binding to stoichiometric CuI allowed the formation of stoichiometric amido copper species, which proved to be efficient in Ullmann coupling with bromoalkynes **38** to deliver ynamides in 40~76% yields (Scheme **14**). The coupling reactions proceeded well with carbamates, sulfonamides, chiral oxazolidinones and chiral imidazolidinones.



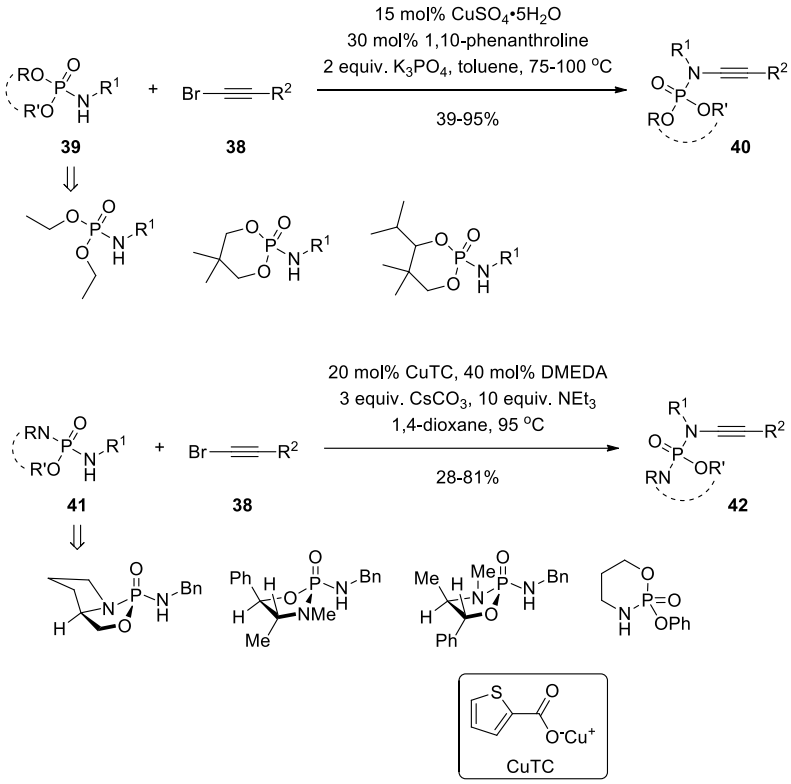
Scheme 14: Modified Ullmann coupling of amides to ynamides.

The $CuSO_4 \cdot 5H_2O$-1,10-phenanthroline complex has been identified as a robust catalyst [26, 27, 28] to promote Ullmann coupling of amides with bromoalkynes under mild heating condition. A wide range of amides could be converted to the corresponding ynamides, including sulfonamides and imidazolidinones. This method overcame the requirement of the harsh heating and strong base (Scheme **15**).



Scheme 15: Modified Ullmann coupling of amides to ynamides.

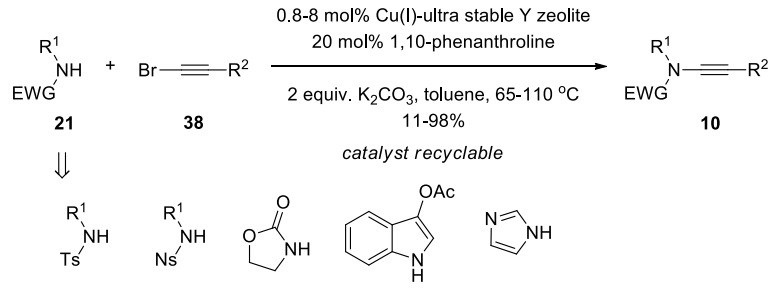
Phosphoramidates have been recognized as the amide surrogates. Hsung *et al* [29] described the first synthesis of *N*-phosphoryl ynamides featuring C- and P-chirality *via* Cu(I)-catalyzed amidative couplings between phosphoramidates **39** and phosphordiamidates **41** with alkynyl bromides **38**, using a readily available catalytic system of a) $CuSO_4•5H_2O$ and 1,10-phenanthroline; b) CuTC and DMEDA (Scheme **16**).



Scheme 16: Synthesis of *N*-phosphoryl ynamides.

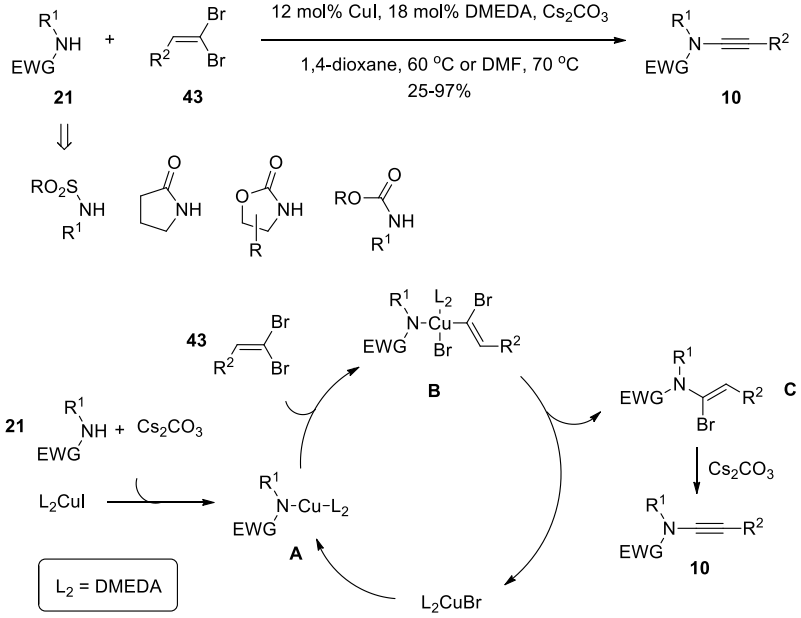
Following Hsung's and Danheiser's homogeneous catalysis, heterogeneous catalysis in Ullman coupling was then investigated by Pale and co-workers [30]. This study investigated the feasibility of reusing or recycling utility of Cu(I)-ultra stable Y zeolite for the coupling of alkynyl bromides **38** and secondary amides **21** (Scheme **17**). This

Cu(I)-ultra stable Y zeolite could be recycled at least five times, with a low loading (0.8-8 mol%) to be a key feature in realizing catalytic turnover.



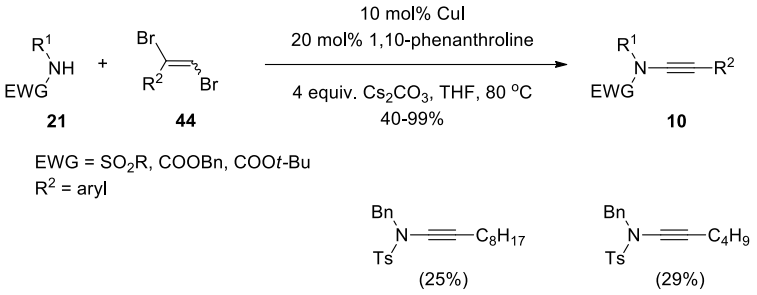
Scheme 17: Synthesis of ynamides with heterogeneous copper catalyst.

Dibromoalkenes, readily prepared from corresponding aldehydes, were identified as alkynyl bromides surrogates in the Ullmann coupling [31]. Such dibromoalkenes could be coupled with various amides in the catalytic system of CuI and DMEDA (Scheme **18**). In the proposed mechanism, amido-copper complex **A** underwent oxidative addition to the less-hindered C-Br bond of the dibromoalkene **43**, followed by amide ligand-exchange and reductive elimination to render (*Z*)-α-bromoenamide **C**, which was validated by control experiment. Subsequent dehydrobromination with Cs_2CO_3 gave the target ynamide **10**. The application of Cs_2CO_3 in 1,4-dioxane or DMF (*N*,*N*-dimethylformamide) was the best condition for the Ullmann coupling. Other choices of bases and solvents would lead to nucleophilic addition of amides onto ynamides [32, 33]. However, acyclic secondary amides or ureas did not give the corresponding ynamides.



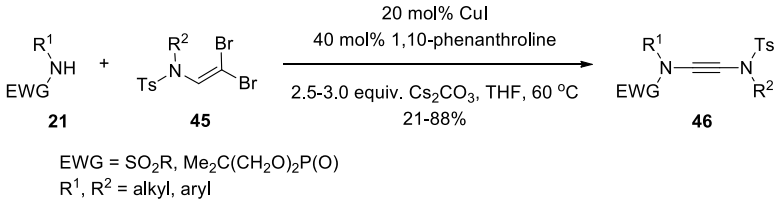
Scheme 18: Synthesis of ynamides from vinyl dibromides and the proposed mechanism.

In the mean time, replacement of 1,1-dibromoalkenes by 1,2-dibromoalkenes **44** with amides afforded ynamides *via* Cu(I)-catalyzed amidative cross-coupling [34] (Scheme **19**). However, aliphatic 1,2-dibromoalkenes were inefficient for the Ullmann coupling, affording ynamides in poor yields (25~29%). Control experiments indicated that dehydrobromination of 1,2-dibromoalkenes occurred and gave alkynyl bromides prior to coupling with amide moieties, which was different from Evano's work.



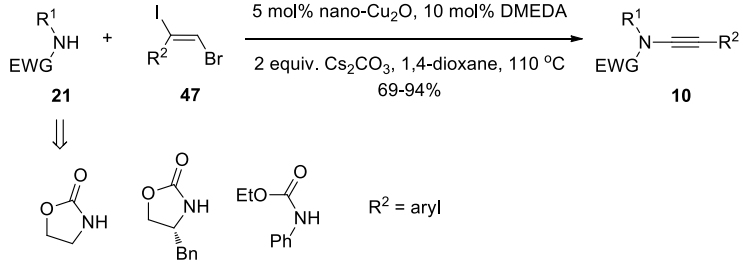
Scheme 19: Synthesis of ynamides from 1,2-dibromo-1-alkenes.

The synthesis and chemistry of yndiamides, acetylenes featuring two amido substituents, is unknown. This class of alkyne would be of considerable interest as a synthetic building block with two nitrogen substituents, yndiamides could exhibit distinct reactivities compared to ynamides. Anderson *et al* [35] has established the first synthetic route to yndiamides **46**, a novel class of *bis*-aza-substituted alkynes, *via* Cu(I)-catalyzed cross-coupling of 1,1-dibromoenamides **45** with nitrogen nucleophiles **21** (Scheme **20**). Their unique reactivities in $Pd(OAc)_2$, $[(C_{10}H_8)Rh(cod)]SbF_6$, $RhCl(PPh_3)_3$, $AuCl(PPh_3)_3$ / $AgSbF_6$, and Brønsted acid-catalyzed cyclizations, suggested significant potential for future applications.



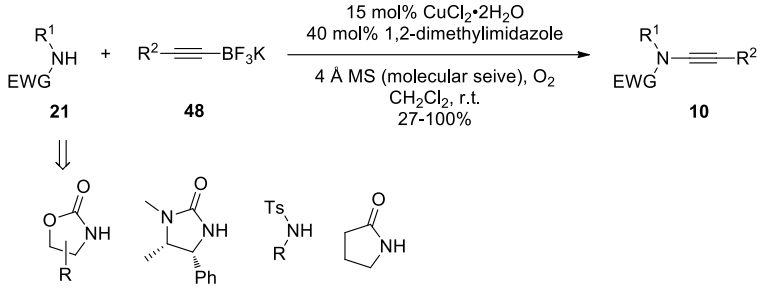
Scheme 20: Synthesis of yndiamides.

(*Z*)-1-Bromo-2-iodoalkenes **47** were also coupled with carbamates (or oxazolidinones) **21** with catalytic nano-Cu_2O-DMEDA complex and delivered corresponding ynamides **10** in good yields [36] (Scheme **21**).



Scheme 21: Synthesis of ynamides from 1-bromo-2-iodoalkenes.

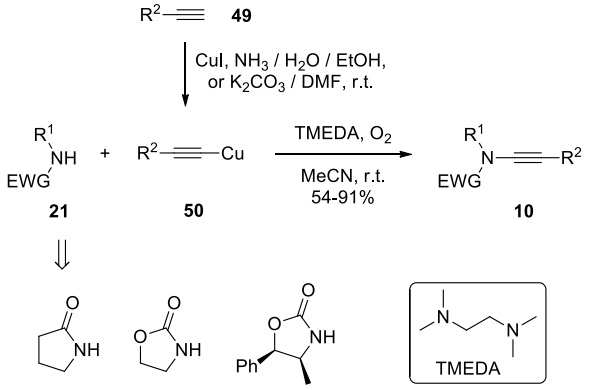
Amidative coupling with potassium alkynyltrifluoroborates **48**, catalyzed by complex of $CuCl_2$•$2H_2O$ and 1,2-dimethylimidazole under base-free conditions proceeded smoothly to give a wide range of ynamides bearing oxazolidinones, imidazolidinones, sulfonamides and lactams [37] (Scheme **22**).



Scheme 22: Synthesis of ynamides from potassium alkynyltrifluoroborate.

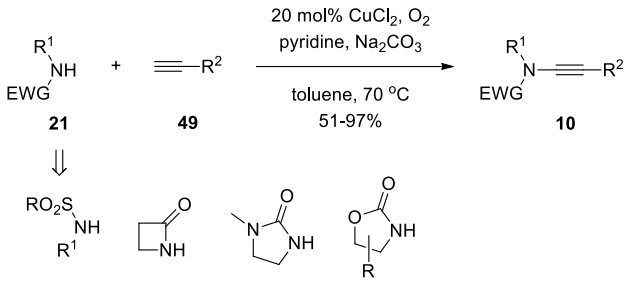
Oxidative coupling

Evano's group developed the methodology of aerobic amidative coupling with copper acetylides [38, 39, 40]. Notably, it obviates the need for a preformed haloalkyne or dihaloalkene. Generated *in situ* by mixing terminal alkynes **49** with CuI, ammonia, and K_2CO_3, the bench-stable copper acetylides **50** readily coupled with oxazolidinones and lactams **21** to furnish the corresponding ynamides **10** at room temperature (Scheme **23**). The reductive copper was then oxidized by oxygen and triggered the next catalytic cycle.



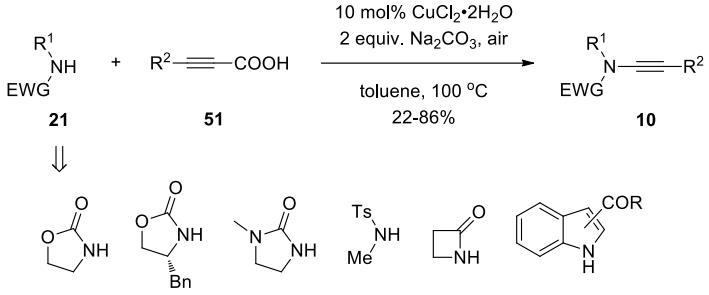
Scheme 23: Synthesis of ynamides from copper acetylides.

Stahl *et al* [41] reported an oxidative amidative coupling with terminal alkynes **49** without utilitizing bromoalkynes under harsh condition (Scheme **24**). Byproducts were minimized by increasing the amount of nitrogen nucleophile **21** to 5 equivalents. The postulated mechanism rationalized the beneficial effect of using excess of the nitrogen nucleophiles: formation of Cu(II) (alkynyl)(amidate) species was expected to compete over the formation of *bis*-alkynyl Cu(II) species.



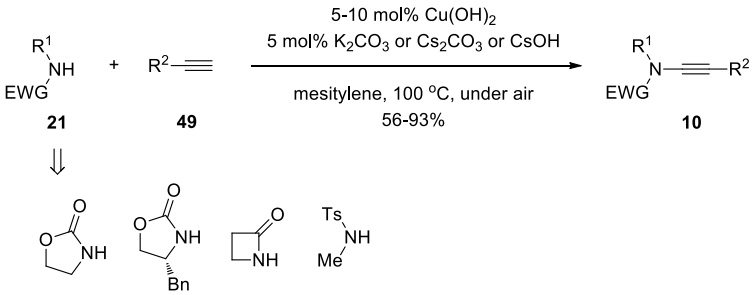
Scheme 24: Synthesis of ynamides from oxidative alkynylation.

Propiolic acids **51** were identified as a bench-stable "masked" terminal alkynes for oxidative coupling to produce ynamides with yields up to 86%, through Cu-catalyzed decarboxylation [42] (Scheme **25**).



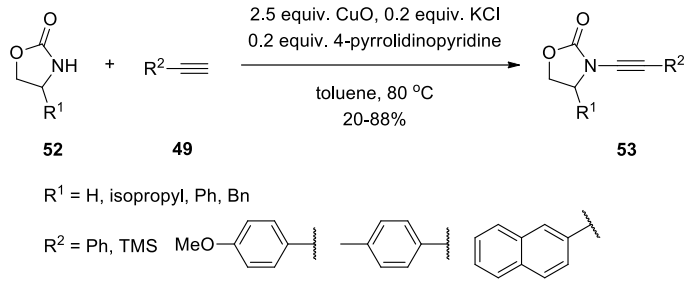
Scheme 25: Synthesis of ynamides from decarboxylative coupling.

Albeit of poor activities in catalyzing homo-coupling, $Cu(OH)_2$ was found to be efficient in oxidative cross-coupling of a broad range of terminal alkynes **49** and amides **21** to give the corresponding ynamides **10** in moderated to high yields, with a low loading of inorganic base (5 mol%) [43] (Scheme **26**). Slow addition of terminal alkynes to the reaction mixture was not required in this protocol.



Scheme 26: Synthesis of ynamides from oxidative coupling.

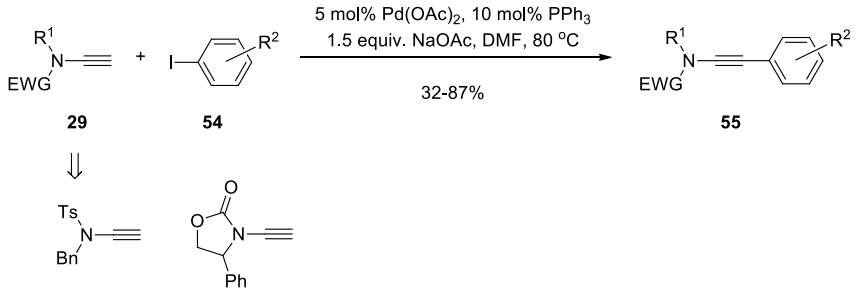
Interestingly, excess of CuO was found to mediate an "oxidative" amidative coupling of terminal alkynes **49** with 2-oxazolidinones **52** in the absence of oxygen [44] (Scheme **27**).



Scheme 27: Synthesis of ynamides from oxidative coupling free of oxygen.

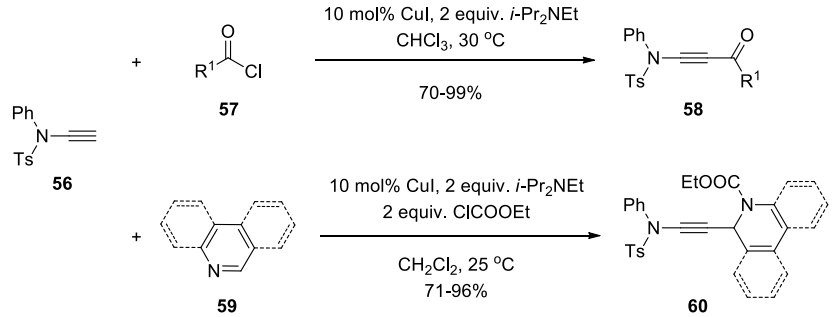
Functionalization of terminal ynamides

Sonogashira reaction is usually a good choice to synthesize substituted alkynes. However, when a standard Sonogashira cross-coupling condition was employed to ynamides, dimerization of ynamides was observed [10]. The first Sonogashira coupling was achieved by Hsung's group *via* a two-step procedure [45] in which CuI was added after mixing a terminal ynamide, aryl halide, and palladium complex in a solvent. After detailed screening, Wakamatsu's group [46] developed an efficient copper-free Sonogashira coupling of terminal ynamides **29** and aryl iodides **54** to provide substituted ynamides **55** (Scheme **28**).



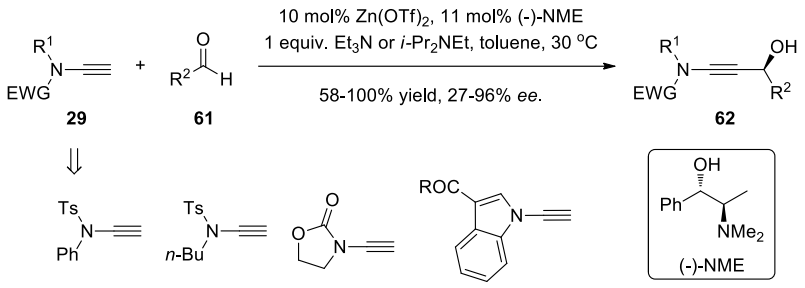
Scheme 28: Synthesis of ynamides from copper-free Sonogashira coupling.

Wolf's group has made efforts to functionalize terminal ynamides [47] by addition of *N*-ethyl-*N*-phenyl-4-tolylsulfonamide **56** to acyl chlorides **57** and *N*-heterocycles **59**, providing a variety of 3-aminoynones **58** and 1,2-dihydro-*N*-heterocycles **60** in high yields, respectively [48] (Scheme **29**).



Scheme 29: Synthesis of amido-ynone.

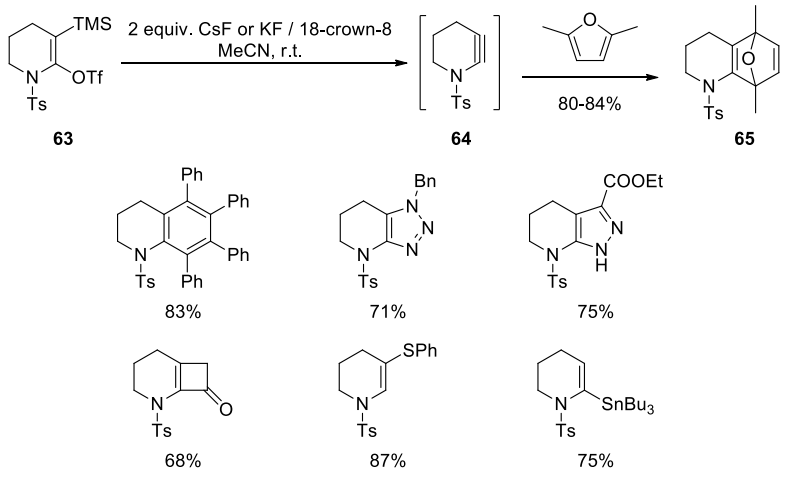
They also developed the catalytic enantioselective addition of terminal ynamides **29** to aldehydes **61** [49]. In the presence of catalytic amounts of $Zn(OTf)_2$ and (-)-*N*-methylephedrine (NME), *N*-substituted propargylic alcohols **62** were formed in good yields and enatioselectivities (Scheme **30**).



Scheme 30: Catalytic enantioselective addition of terminal ynamides to aldehydes.

Strained cyclic ynamide

Danheiser's group [50] reported the first synthesis of a strained six-membered cyclic ynamide. *N*-tosyl-3-azacyclohexyne **64** was generated *via* fluoride-promoted 1,2-elimination of the precursor **63**. Diels-Alder adduct **65** was formed after adding dimethylfuran as the trapping agent, which demonstrated the existence of the strained cyclic ynamide. Various nitrogen heterocyclic compounds could be obtained when different reaction partners were used (Scheme **31**).



Scheme 31: Diels-Alder reactions of *N*-tosyl-3-azacyclohexynes with dienes.

REACTIONS OF YNAMIDES

The first decade of 21st century witnessed the fast growing of ynamide chemistry investigation. Many new transformations have been found during the investigation. In the second decade, researchers keep exploring more to reveal the value of ynamides. This section will discuss the recent advances of reactions of ynamides, including addition, nucleo-metallation, rearrangement, cyclization, and cycloaddition.

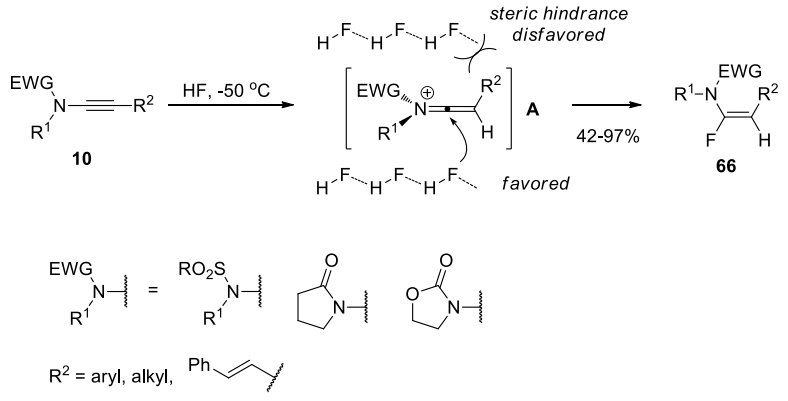
Addition Reaction

The electrophilicity of α-carbon and nucleophilicity of β-carbon of ynamides allow regioselective addition of nucleophiles or electrophiles onto the triple bond.

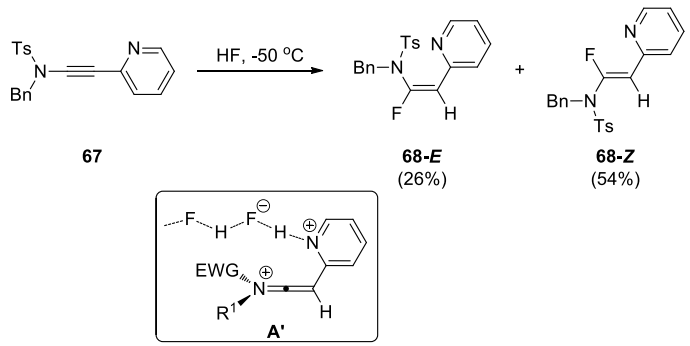
Addition to α-position of ynamides

With carbon-halogen bond formation

Evano, Thibaudeau and co-workers reported a highly regio- and stereo-selective synthesis of α-fluoroenamides through a hydrofluorination of ynamides in a superacid medium [51]. At first, they found that with the presence of appropriate amount of antimony pentafluoride (SbF_5), the ionic composition of HF-SbF_5 could drive the desired reaction to generate α-fluoroenamides. Later, they found that by using anhydrous superacid HF without SbF_5, the hydrofluorination performed more efficiently to achieve 96% yield in 5 minutes in -50 ^oC. The anhydrous superacid HF allowed the formation of highly reactive keteniminium intermediate and subsequent fluorination and minimized undesired side reactions (*e.g*. hydrolysis). A wide range of substrates were tolerated, including aryl, alkyl, alkenyl substituted ynesulfonamides, alkynyl carbamates and lactams. This hydrofluorination turned out to be highly stereoselective with (*E*)-α-fluoroenamides **66** as dominant products (Scheme **32**). With regard to keteniminium **A**, the steric hindrance between the substituent and the HF chain favored the addition of F^- at *trans*-position of R^2. When a directing group was introduced, this stereoselectivity could be tuned. 2-Pyridinyl substituted ynesulfonamide **67** gave (*Z*)-α-fluoroenesulfonamide **68** as the main product, which might be attributed to the fluorine-ammonium electrostatic interaction (Scheme **33**).

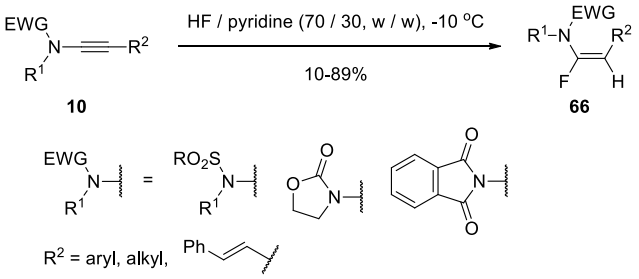


Scheme 32: Hydrofluorination of ynamides in anhydrous HF.



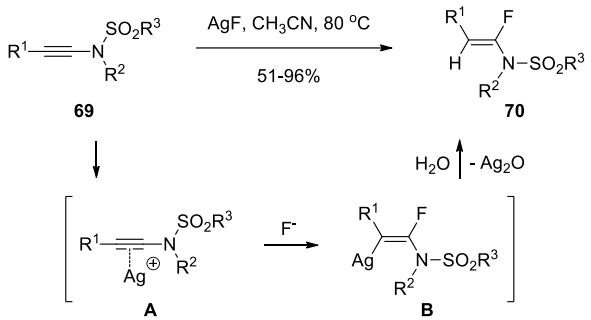
Scheme 33: Ammonium assisted hydrofluorination of 2-pyridinyl substituted ynesulfonamides.

As bioisosteres of ureas, α-fluoroenamides could become powerful building blocks for biological and medicinal studies. Evano, Thibaudeau and co-workers continued to investigate hydrofluorination of ynamides [52] using the mixture of HF / pyridine (70 / 30, w / w). The new process avoided handling pure liquid HF and thus allowed the hydrofluorination of some ynamides which could not work in pure HF (Scheme **34**).



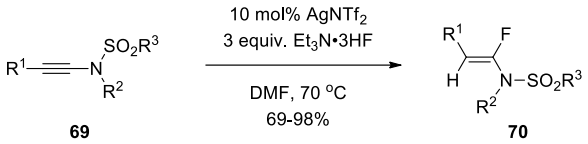
Scheme 34: Hydrofluorination of ynamides in HF/pyridine.

Zheng, Zhu and co-workers [53] discovered that a new type of fluorination reagent, silver fluoride (AgF), could realize the hydrofluorination of ynesulfonamides **69** to render (*Z*)-α-fluoroenamides **70** in good yields, compared with (*E*)-counterparts using HF condition. After activation of triple bond by Ag^+, F^- added to the α-carbon of ynamides from the back side of Ag^+ to generate intermediate **B.** Further hydrolysis of **B** finally delivered product **70** (Scheme **35**).



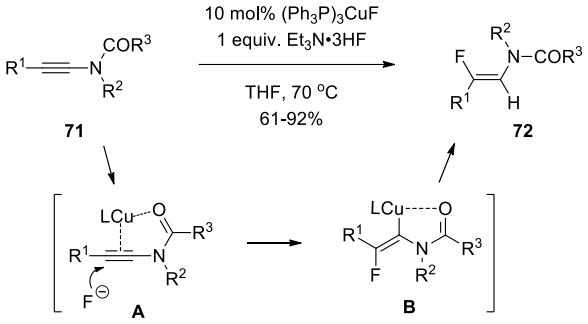
Scheme 35: Silver promoted *trans*-hydrofluorination of ynesulfonamides.

Zhu's group [54] reported $AgNTf_2$ catalyzed *trans*-hydrofluorination of ynamides with Et_3N•3HF as the fluorine source, giving The (*Z*)-α-fluoroenamides **70** as the dominant products in good yields (Scheme **36**).



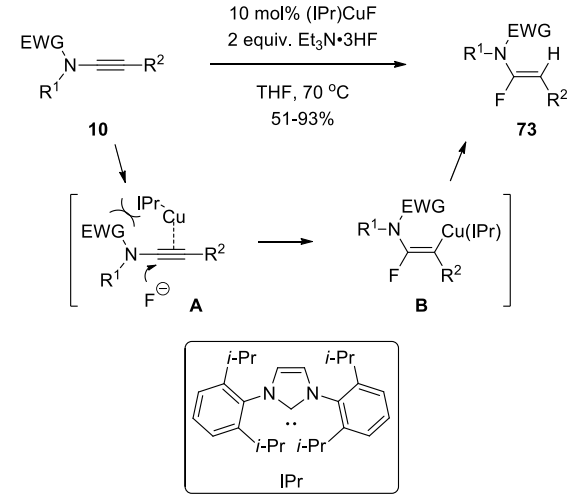
Scheme 36: Ag catalyzed *trans*-hydrofluorination of ynamides.

It was noticeable that the regioselectivity of fluorination of ynamides was inversed when replacing $AgNTf_2$ with $(PPh_3)_3CuF$, presumably due to the existing 5-membered-chelation between Cu and amide groups (Scheme **37**).



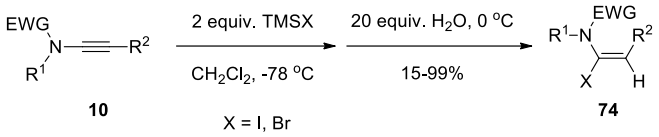
Scheme 37: Cu catalyzed *trans*-hydrofluorination of ynamides.

Interestingly, later report [55] showed that the inverse regioselecvitity of hydrofluorination of ynamides was observed in the case of (IPr)CuF, with the explanation that the coordination between the Cu center and the carbonyl group of ynamides was disfavored arising from the steric hindrance of IPr group (Scheme **38**).



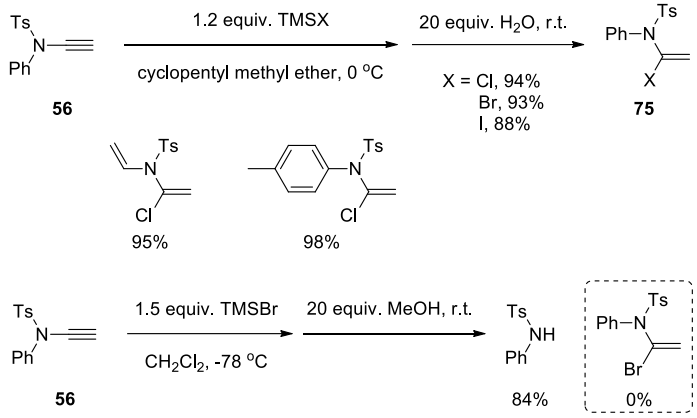
Scheme 38: Cu catalyzed *trans*-hydrofluorination of ynamides.

As for hydrochlorination, Iwasawa *et al* [56] reported a facile, metal-free approach to prepare α-haloenamides **74** by the addition of *in situ* generated HX (X = I or Br) to ynamides (Scheme **39**) *via* quenching the mixture of TMSX and ynamides with 20 equivalents of water.



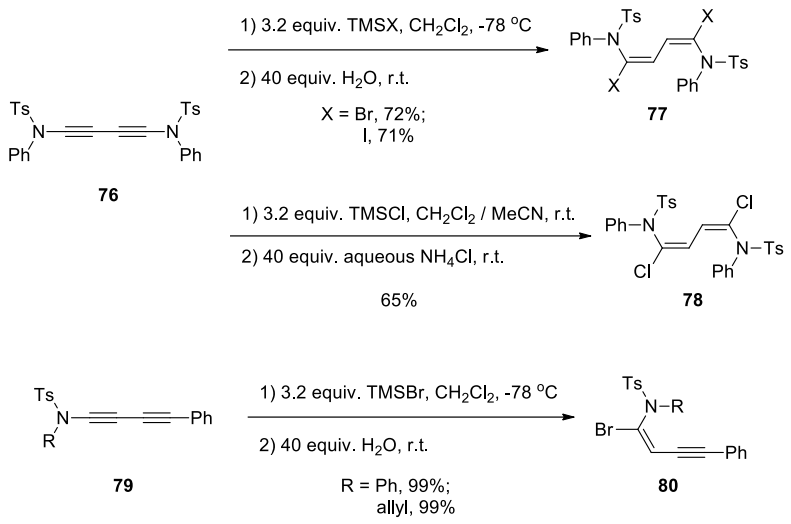
Scheme 39: Hydroiodation and hydrobromination of ynamides.

This approach also worked for terminal ynamides [57]. The *in situ* HX, generated from TMSX (X = Cl, Br, I) and 20 equivalents of water, could add to terminal ynamides **56** and form 1-haloethenamides **75** (Scheme **40**). Water served as the key proton source, whereas C-N cleavage was observed when replacing water with methanol.



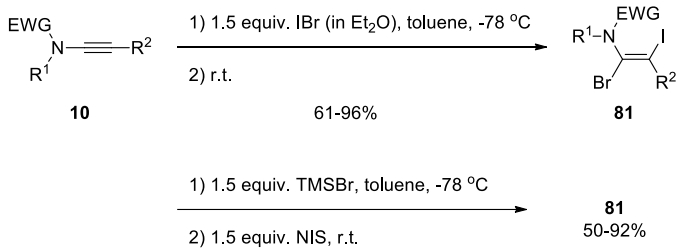
Scheme 40: Hydrohalogenation of terminal ynamides.

As for the conjugated ynamides (buta-1,3-diyne-1,4-diamides), the regio- and stereoselective hydrohalogenation proceeded under the same approach [58]. The authors pointed out that the combination of TMSCl and water failed to generate the desired product. A successful hydrochlorination required aqueous NH_4Cl, which would increase the concentration of chloride in the system, rather than water (Scheme **41**). The study of unsymetrically 1,3-diyne **79** also demonstrated an excellent chemoselective hydrobromination of ynamide in presence of the alkyne.



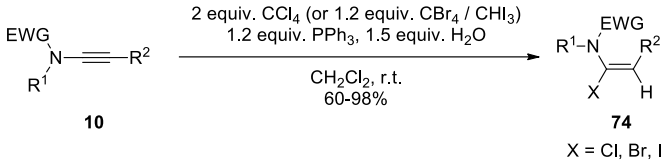
Scheme 41: Hydrohalogenation of conjugated ynamides.

Iodobromine, with negative charged bromine and positive charged iodine, could add to ynamides to form (*E*)-α-bromo-β-iodoenamides. Iwasawa's group [59] proved that this regio- and stereoselective iodobromination proceeded well with commercially available IBr. To improve the handling convenience, they found the combination of TMSBr and NIS (*N*-iodosuccinimide), which could generate IBr *in situ*, drove the iodobromination of ynamides to proceed efficiently as well (Scheme **42**).

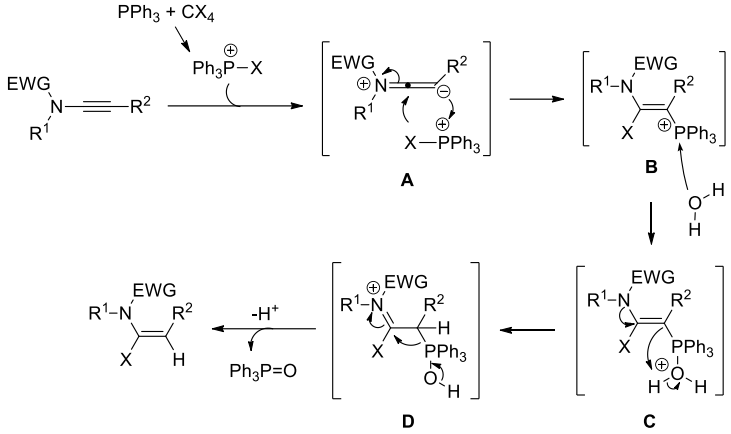


Scheme 42: Iodobromination of ynamides**.**

Sahoo's group [60] developed another metal-free hydrohalogenation of ynamides by using halophosphonium salts which were generated *in situ* from Ph_3P and CCl_4, CBr_4 or CHI_3. The hydrohalogenation once again showed high regio- and stereoselectivity to afford (*E*)-α-haloenamides **74** as the major product (Scheme **43**). The reaction worked well at room temperature in good-to-excellent yields. It was proposed that the phosphonium salt first added to the ynamide substrate in a concerted manner to yield cationic β-phosphonium-α-haloenamide intermediate **B**. The nucleophilic attack of water to the cationic intermediate **B** generated the intermediate **C**. After the proton transfer and the release of triphenylphosphine oxide (supported by the ^{31}P NMR monitoring), (*E*)-α-haloenamide was formed as the major product (Scheme **44**).

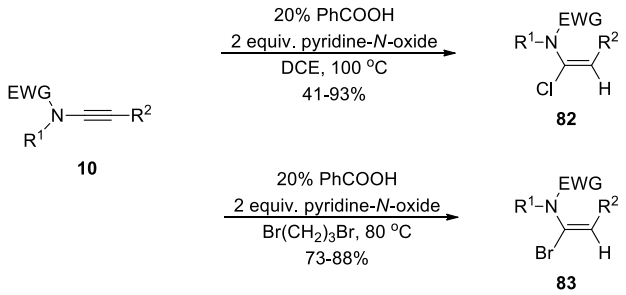


Scheme 43: Hydrohalogenation of ynamides.



Scheme 44: Plausible mechanistic path.

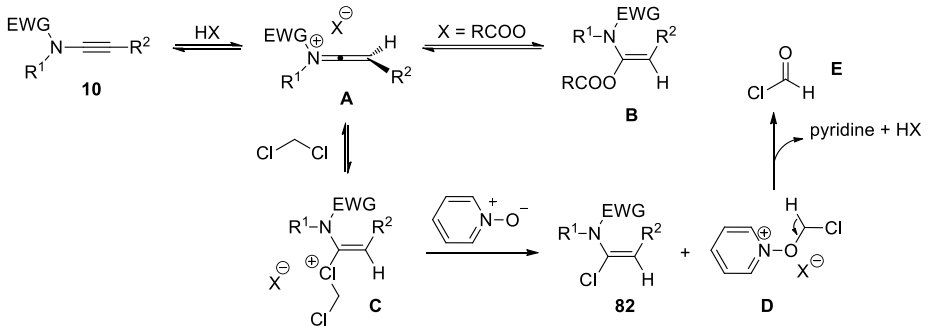
Shin's group [61] reported a novel synthesis of α-haloenamides with halogenated solvents and pyridine-*N*-oxide (Scheme **45**). The halogen source in this synthesis was halogenated solvents (*e.g.* dichloromethane, dibromomethane, *etc*). DCE (1,2-dichloroethane) and 1,3-dibromopropane were found to be the most suitable solvents for the chlorination and bromination, respectively, due to the optimal balance between the reaction rate and the yield. A series of Brønsted acids could trigger the reaction, and benzoic acid was the optimal one. Pyridine-*N*-oxide was an essential additive to trigger hydrohalogenation. Noticeably, electron-donating group substituted pyridine-*N*-oxides led to lower yields and the electron-withdrawing substituted ones led to a very slow reaction.



Scheme 45: α-Halogenation of ynamides from halogenated solvents and pyridine-*N*-oxide.

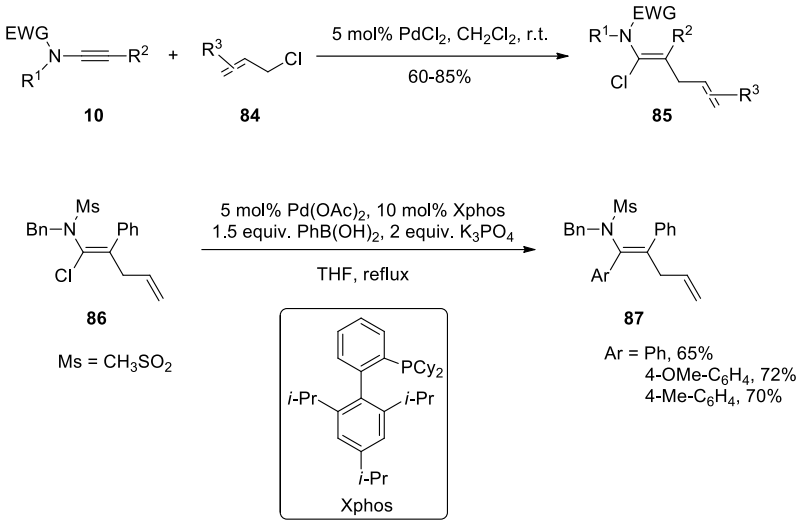
The Brønsted acid HX first added to substrate to form keteniminium intermediate **A**. In the absence of pyridine-*N*-oxide, the nucleophilic anion X could further attack the intermediate **A** to generate the ynamide-acid adduct **B**, which was demonstrated by

the control experiments. When pyridine-*N*-oxide was present, those steps could be reversed by trapping keteniminium **A** by the halogenated solvent into halonium intermediate **C**. The substitution of chloromethine by pyridine-*N*-oxide delivered the desired α-haloenamide product, with the remaining **D** deprotonated into the aldehyde **E** (Scheme **46**).



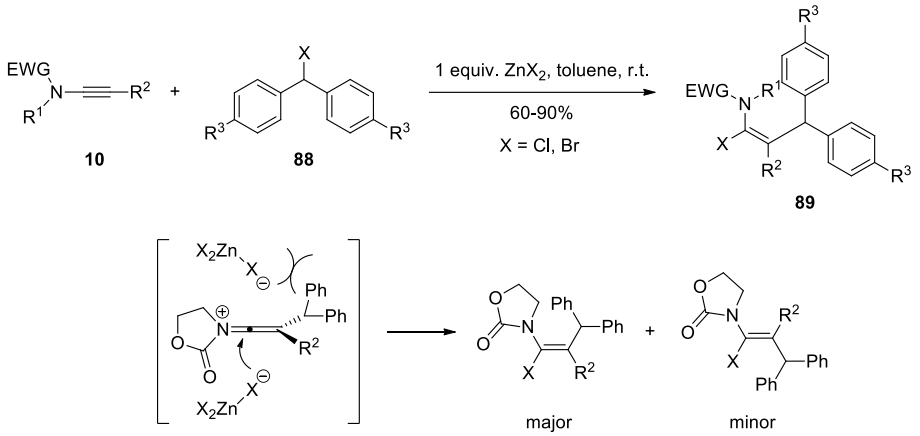
Scheme 46: The proposed mechanism of α-halogenation.

Allyl and benzyl halides could also be used to realize the α-halogenation of ynamides. Zhu's group [62] reported chloro-allylation of ynamides catalyzed by $PdCl_2$ at room temperature in good yields, during which process, α-C-Cl bond and β-C-C bond were formed simultaneously (Scheme **47**). The resulting α-chloroenamide **86** could further undergo a Suzuki coupling to provide tetrasubstituted enamides **87**.



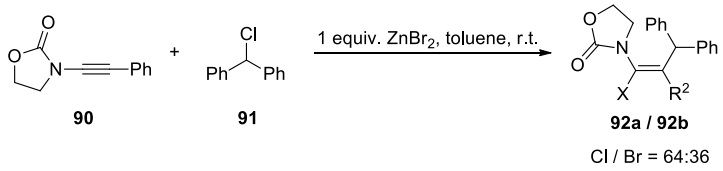
Scheme 47: Chloroallylation of ynamides and Suzuki coupling of α-chloroenamide.

Cao's group [63] found that with stoichiometric $ZnCl_2$ (or $ZnBr_2$), the addition of benzhydryl chloride (or bromide) **88** to ynamide proceeded smoothly in good yields (Scheme **48**). Benzyl chloride, benzyl bromide, and trityl chloride were inactive under this condition. The steric hindrance between benzhydryl group and the Zn-ynamide complex favored the *trans*-carbohalogenation.



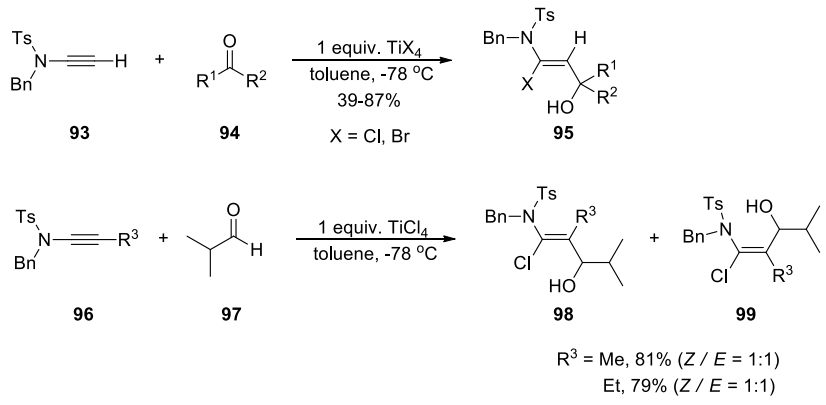
Scheme 48: Addition of benzhydryl halides to ynamides.

The cross-reaction experiment showed that the halogen in the α-haloenamide came from both benzhydryl halide and the Lewis acid. In the $ZnBr_2$ mediated reaction of benzhydryl chloride **91** and ynamide **90**, α-chloroenamide **92a** and α-bromoenamide **92b** were both detected in a ratio of 64:36 (Scheme **49**).



Scheme 49: The cross-reaction with benzhydryl chloride and $ZnBr_2$.

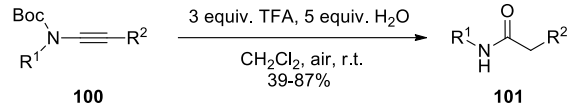
By using an aldehyde or a ketone as the electrophile to trap the keteniminium intermediate, Matsuo's group [64] developed a new approach to achieve α-halogenation and β-C-C bond formation of *N*-sulfonylynamides in one reaction. The reaction occurred smoothly with stoichiometric $TiCl_4$ (or $TiBr_4$) as halide source at -78 °C (Scheme **50**). Terminal *N*-sulfonylynamides **93** could be converted to (*Z*)-α-halo-γ-hydroxyenamides **95** in moderate to good yields stereoselectively. When the substrate was changed to the internal ynamide **96**, the product was a mixture of *Z* / *E* isomers **98** and **99** (*Z* / *E* = 1 : 1).



Scheme 50: TiX_4 mediated addition of aldehydes or ketones to ynamides.

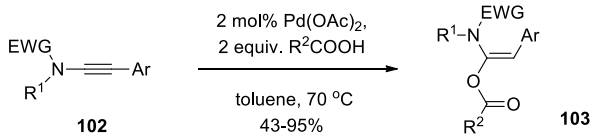
With carbon-oxygen bond formation

In the synthesis or functionalization of ynamides, a hydration would generate undesired amide by-products. Zhu's group [65] found that the Boc (*N*-*tert*-butyloxycarbonyl) substibuted ynamides **100** underwent a hydration in TFA (trifluoroacetic acid) at room temperature to afford the *N*-monosubstituted amides **101** in high yields (Scheme **51**). The Boc group was removed in the acidic conditions at the same time. Other kinds of ynamides (oxazolidinone, sulfonamide, and carbamate) were not able to convert into the corresponding amides under TFA condition.



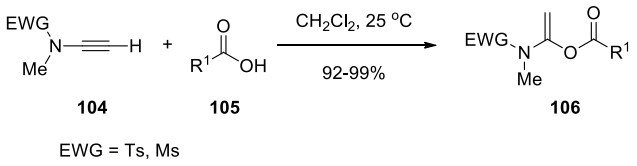
Scheme 51: TFA mediated hydration of ynamides.

The hydroacyloxylation of ynamides with carboxylic acids could form α-acyloxyenamides. Lam and co-workers [66] developed the first palladium catalyzed hydroacyloxylation of ynamides (Scheme **52**). (*E*)-α-acyloxyenamides **103** were synthesized in moderate to good yields. A diverse range of carboxylic acids and various aryl-substituted ynamides were tolerated.

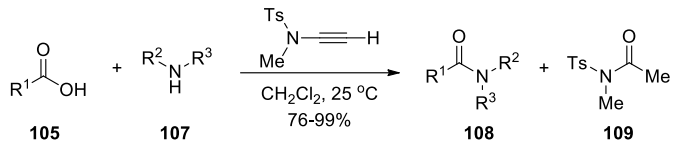


Scheme 52: Hydroacyloxylation of ynamides.

Zhao's group [67] found that when *N*-methylynemethyl sulfonamide (MYMsA) or *N*-methylynetoluene sulfonamide (MYTsA) was used as the substrate, the addition of a series of carboxylic acids gave α-acyloxyenamides **106** nearly quantitatively (92~99%) at room temperature without any catalyst (Scheme **53**). α-Acyloxyenamides could undergo amidation conveniently in the presence of aliphatic amines (Scheme **54**). Secondary amines reacted with α-acyloxyenamides faster than primary ones due to the increased nucleophilicity. By contrast, aryl amines were inert to amidation.

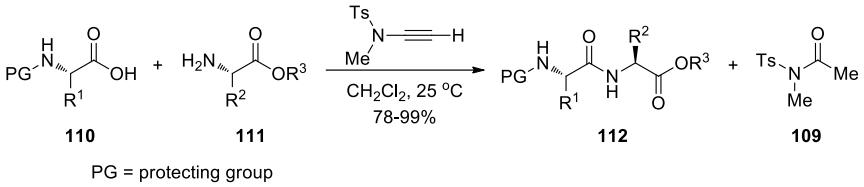


Scheme 53: Hydroacyloxylation of ynamides.



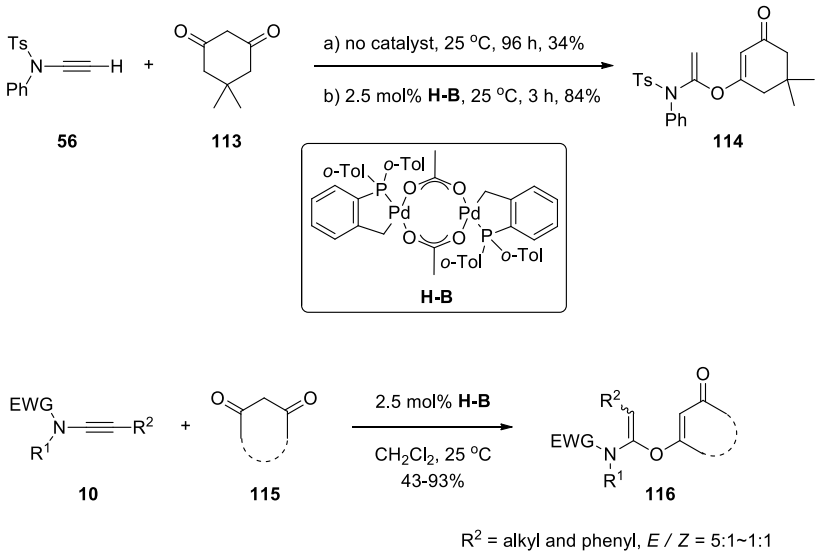
Scheme 54: MYTsA-mediated amide bond formation between carboxylic acids and amines.

The authors combined these two reactions into a highly efficient, one-pot strategy to prepare peptides, in which MYMsA and MYTsA worked as crucial coupling reagents. All the chirality of the aminoacids (**110** and **111**) was well preserved under this one-pot synthesis, and no epimerization or racemization was detected in the peptide products **112** (Scheme **55**).



Scheme 55: MYTsA-mediated peptide bond formation.

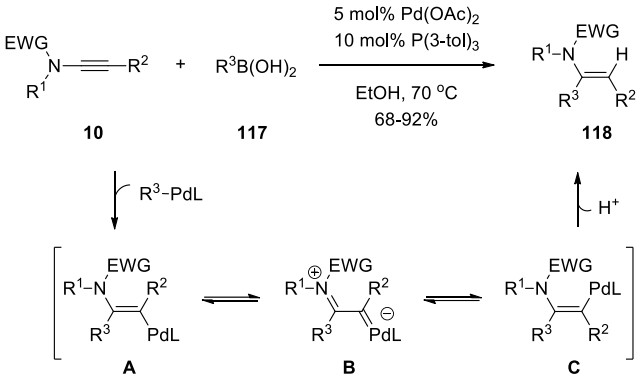
Clavier and co-workers [68] found that dimedone **113** could add to ynesulfonamide **56** to form α-alkoxyenamide **114** without catalyst in 34% yield after 96 h. By using Herrmann-Beller phosphapalladacycle (**H-B**) as the catalyst, the reaction rate and yield notably increased (Scheme **56**). This addition showed excellent regioselectivity and various 1,3-diones were suitable nucleophiles to build α-C-O bonds. When internal ynamides were used as the substrates, the enamide products were a mixture of *E* and *Z* isomers, in which (*E*)-enamides were more favorable.



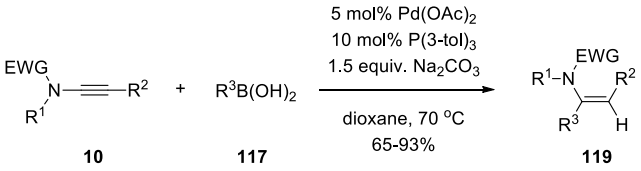
Scheme 56: Addition of 1,3-diones to ynamides.

With carbon-carbon bond formation

To construct C-C bond *via* addition is another important functionalization of ynamides. Zhu's group [69] reported that with $Pd(OAc)_2$ as the catalyst and $P(3\text{-tol})_3$ as the ligand, the aryl group in the boronic acid could add to the C-C triple bond of the ynamide *via trans*-metalation in mild condition. This addition had an excellent α regioselectivity and a high stereoselectivity. (*E*)-enamides **118** were the major products, indicating that there was an isomerization from intermediate **A** to **C** *via* the palladium carbene species **B** before protonolysis of the alkenyl C-Pd bond of intermediate **C** (Scheme **57**). Later work [70] showed that when Na_2CO_3 was applied in this Pd-catalyzed addition, (*Z*)-enamides **119** turned out to be the major products (Scheme **58**), indicating the isomerization of alkenyl palladium intermediate was disfavored.

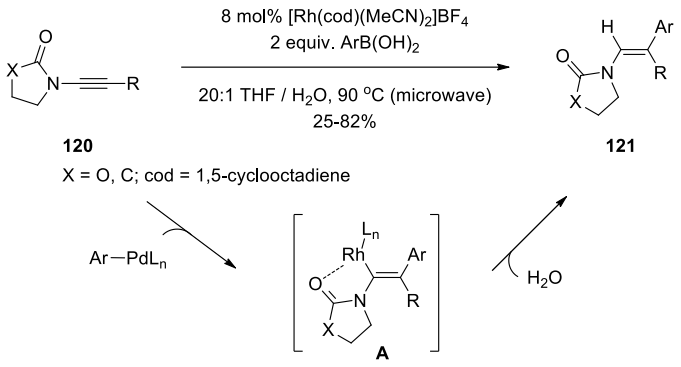


Scheme 57: *Trans*-hydrocarbonation of ynamides.



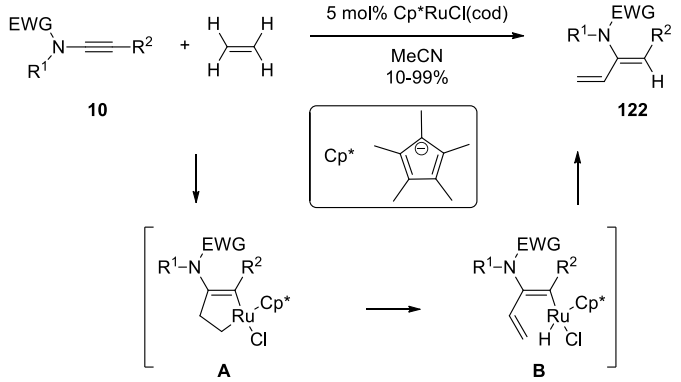
Scheme 58: *Cis*-hydrocarbonation of ynamides.

The regioselectivity was inversed in Lam's pioneering work [71] on the hydroarylation of ynamides, by taking advantage of the coordination between carbonyl oxygen of the oxazolidinonylynamide and rhodium catalyst, the aryl group favorably added to the β-carbon of ynamide triple bond and generated β,β-disubstituted enamides **121** (Scheme **59**).



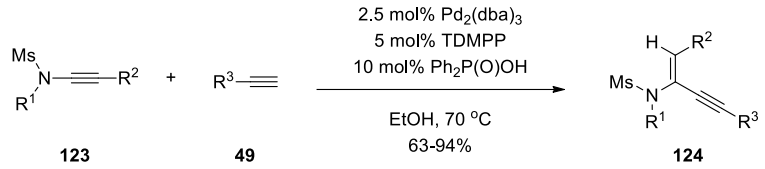
Scheme 59: Rhodium catalyzed hydroarylation of ynamides.

Hydrovinylation or hydroalkynylation of C-C triple bonds is an atom-economical approach to stereoselectively assemble 1,3-dienes or 1,3-enynes, which can serve as useful precursors to construct conjugated polyenenamides. Saito, Sato, and co-workers [72] reported that by using Cp*RuCl(cod) as catalyst, ethylene and ynamides underwent a hydrovinylation-type cross-coupling to give 2-aminobuta-1,3-diene derivatives **122**. The excellent regioselectivity and stereoselectivity were attributed to formation of ruthenacyclopentene intermediate **A** (Scheme **60**).



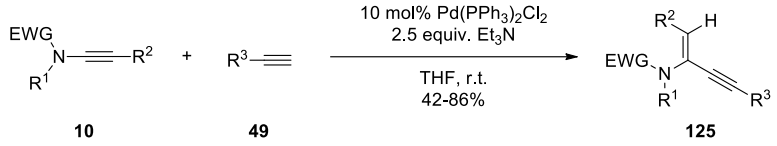
Scheme 60: Ruthenium catalyzed coupling of ynamides and ethylene.

Zhu's group [73] achieved a Pd-catalyzed *trans*-hydroalkynylation of *N*-sulfonylynamides. With $Pd_2(dba)_3$ as the catalyst, tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as the ligand, $Ph_2P(O)OH$ as the additive, and ethanol as the solvent, a series of alkyl and aryl substituted terminal alkynes **49** could add to the *N*-sulfonylynamides **123** with excellent α-regioselectivity in good yields (Scheme **61**). The resulting C-C double bonds were mainly *E* configuration.

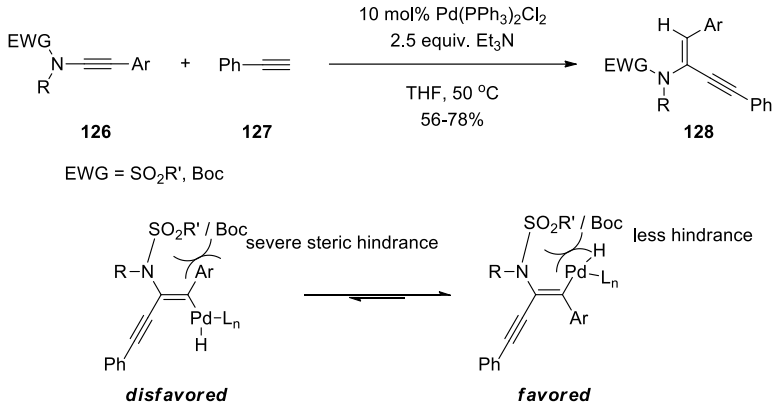


Scheme 61: *Trans*-hydroalkynylation reaction of ynamides.

Reddy and co-workers [74] used $Pd(PPh_3)_2Cl_2$ as the catalyst and triethylamine as the base to realize *cis*-hydroalkynylation of oxazolidinone, lactam, and sulfonyl substituted ynamides (Scheme **62**). They also found that when the ynamide had aryl substitution on the C-C triple bond and sulfonyl / Boc substitution on the nitrogen atom, the Pd intermediate would suffer a severe steric hindrance between these two substituents, which led to a rotation along the forming C-C double bond and generated *Z* configurated adduct eventually (Scheme **63**).



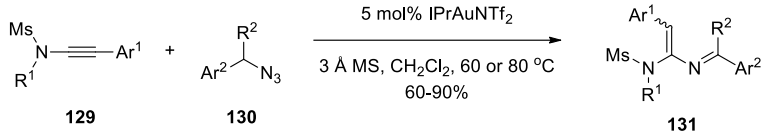
Scheme 62: *Cis*-hydroalkynylation of ynamides.



Scheme 63: *Trans*-hydroalkynylation of aryl substituted ynamides.

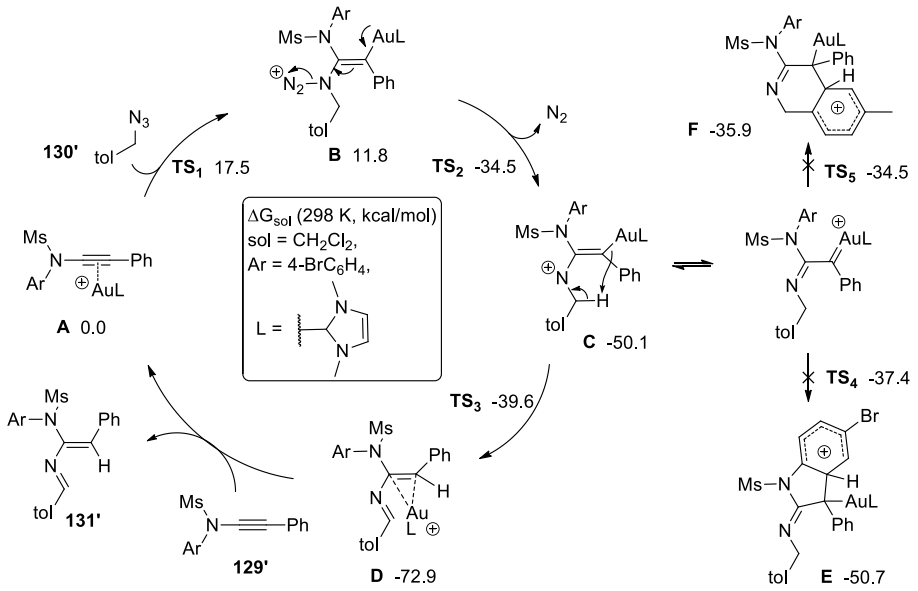
With carbon-nitrogen bond formation

Lu, Ye, and co-workers [75] developed a novel gold-catalyzed tandem intermolecular ynamide amination and C-H functionalization. A variety of highly functionalized 2-aza-1,3-butadienes **131** were obtained with $IPrAuNTf_2$ as the optimal catalyst and azides as the amination reagent. The newly formed C-C double bond in the product had a high *Z* stereoselectivity under optimized reaction conditions (Scheme **64**).



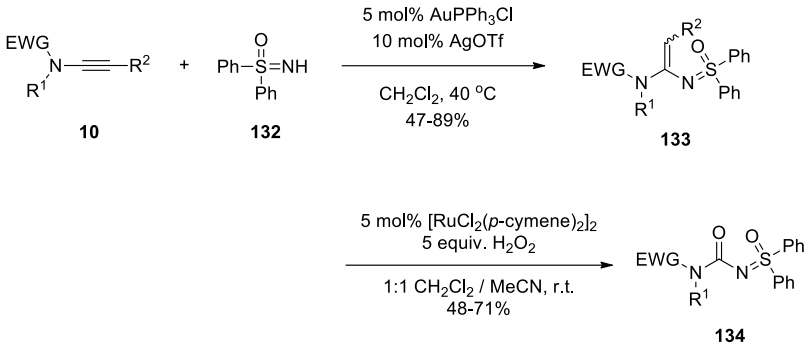
Scheme 64: Amination / C-H Functionalization of ynamides.

The reaction pathway was rationalized with assistance of computation. Azide **130'** attacked the α-position of Au-activated C-C triple bond of the *N*-sulfonylynamide to form the Au-substituted alkene intermediate **B**. Subsequent release of N_2 gave the Au carbene intermediate **C**, which underwent a concerted deprotonation and protodeauration to generate intermediate **D** with a barrier of 10.5 kcal/mol. However, the transformation from intermediate **C** to intermediates **E** and **F** experienced a barrier of 12.7 kcal/mol and 15.6 kcal/mol, respectively, indicating the insertion of the gold carbene moiety to the C-H bond of 4-Br-phenyl or 4-Me-phenyl group was less favored. Therefore, after ligand exchange with intermediate **D**, the product **131'** was generated rather than other kinds of products (Scheme **65**).



Scheme 65: Computed reaction pathway.

Using *N*-H-sulfoximine **132** as the amination reagent, Chen, Wang, and co-workers [76] developed a Au / Ag-cocatalyzed hydrosulfoximination reaction of ynamides to produce the *N*-alkenylated sulfoximidoyl derivatives **133** with *E* isomer as the main product (Scheme **66**). The authors further demonstrated that the C-C double bond of the *N*-alkenylated sulfoximidoyl derivatives **133** could be cleaved under Ru-catalyzed oxidative conditions to afford urea-type sulfoximines **134**, which were interesting building blocks in medicinal chemistry.

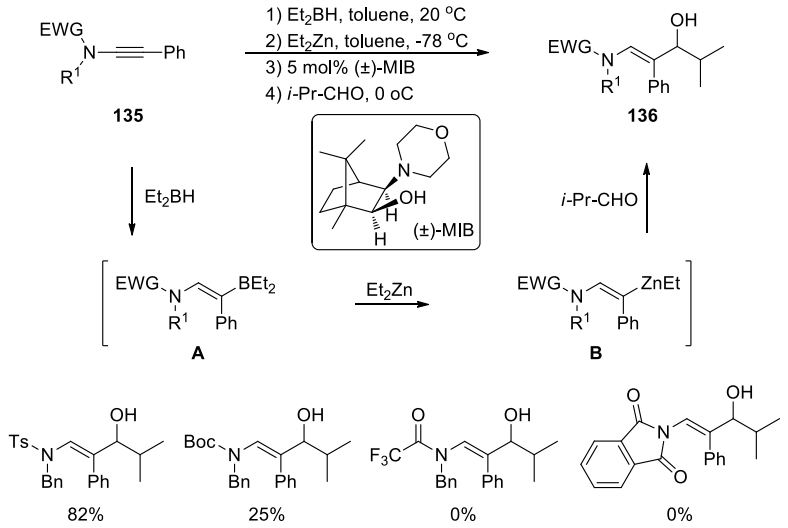


Scheme 66: Hydrosulfoximination and oxidation reactions of ynamides.

Addition to β-position of ynamides

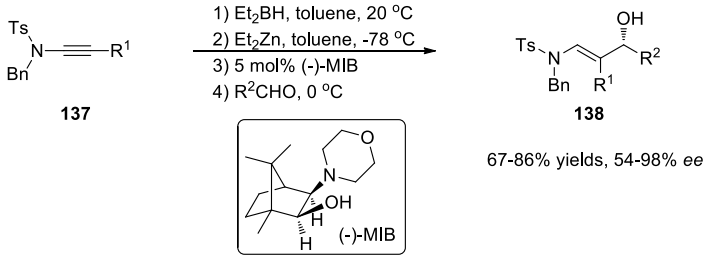
With carbon-boron bond formation

The addition at the β position of ynamides usually requires suitable electrophiles and metallic species. Organoboranes, with electron deficient boron center, were one kind of such electrophiles. Walsh *et al* [77] used diethylborane to achieve hydroxyalkylation of ynamides at the β-position (Scheme **67**). Diethylborane first underwent a *cis*-hydroboration of ynamides **135** to form β-amino vinyl boranes **A** at room temperature. Subsequent boron-to-zinc transmetalation with diethyl zinc generated vinyl zinc intermediates **B**, which reacted with aldehydes to transform into the desired β-hydroxyalkylenamides **136**. The *N*-tosyl substituted ynamides were proven to be the most robust in this tandem reaction. Other ynamides with Boc, trifluoroacetyl, or imide subsitituent turned out to be more sluggish.



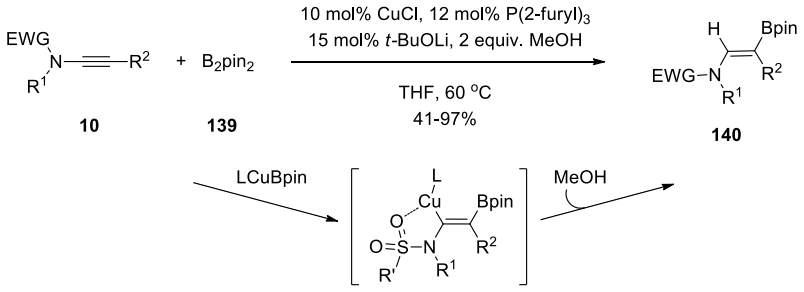
Scheme 67: Hydroxyalkylation of ynamides.

When enantiomerically pure amino alcohol (-)-MIB was used as the catalyst during the addition to aldehydes, asymmetric products **138** with high enantioselectivities (> 90% *ee* mostly) were obtained in good yields (Scheme **68**).



Scheme 68: Asymmetric generation of (*E*)-trisubstituted β–hydroxy enamides.

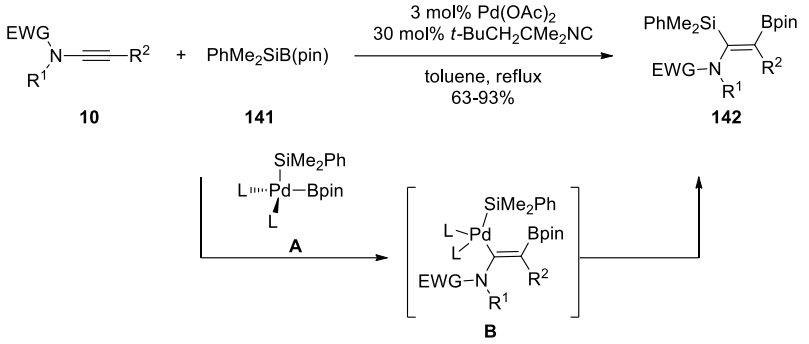
Bis(pinacolato)diboron (B_2pin_2) was a widely used reagent in Cu-catalyzed hydrobroation process. In the catalytic cycle, the copper boryl complex [LCuBpin], generated from transmetalation between Cu catalyst and B_2pin_2, was the key active species which made functionalization of C-C triple bond happen. Zhu, Bai, and co-workers [78] found that with CuCl as the catalyst, $P(2\text{-furyl})_3$ as the ligand, *t*-BuOLi as the base, 2 equivalents of methanol as the additive, and THF as the solvent, a series of ynamides underwent a highly β-selective borylation in good yields (Scheme **69**). Ligand and base had notable effects on the regioselectivity. The combination of phosphorus ligands (*e.g.* PPh_3, $P(o\text{-tol})_3$, $P(m\text{-tol})_3$, $P(p\text{-tol})_3$, $P(p\text{-OMePh})_3$, Xantphos, DPEphos) and *t*-BuONa favored the β-borylation, which had also been observed and been developed into an efficient methodology by other researchers [79].



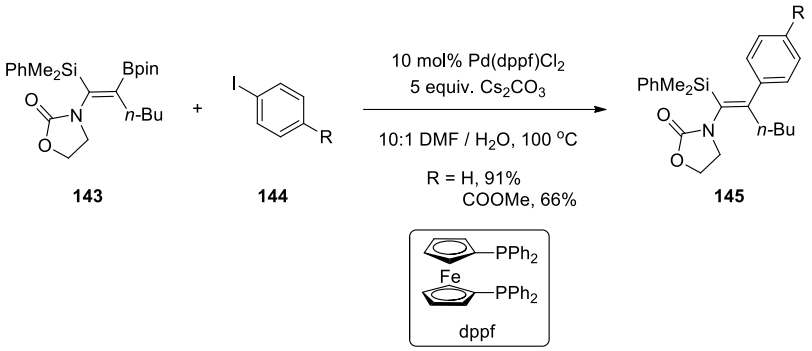
Scheme 69: Copper-catalyzed β-hydroborylation of ynamides.

Silylboranes were another kind of reagent to achieve borylation of ynamides. By using commercially available (dimethylphenylsilyl)pinacolatoboron [$PhMe_2SiB(pin)$], Saito, Sato, and co-workers [80] developed a Pd-catalyzed regioselective silaboration of ynamides that led to formation of silyl- and boryl-substituted enamides. In the catalytic cycle, oxidative addition of $PhMe_2SiB(pin)$ by Pd(0) formed silyl boryl Pd complex **A** with appropriate ligand (*e.g.* isonitrile ligand *t*-$BuCH_2CMe_2NC$), followed by which, the insertion of the C-C triple bond into the Pd-B σ-bond formed the intermediate **B**. The experimental results indicated this insertion step was regioselective and borylation at β position was favored. Subsequent reductive elimination formed the new C-Si bond to generate the silaborated product (Scheme **70**). The silaboratedenamide **143** was further utilized as a coupling partner in

Suzuki-Miyaura coupling reaction. The corresponding coupling products **145** were obtained in good yields (Scheme **71**). The borylation of ynamides served as an efficient approach for further C-C bond formation at β position.



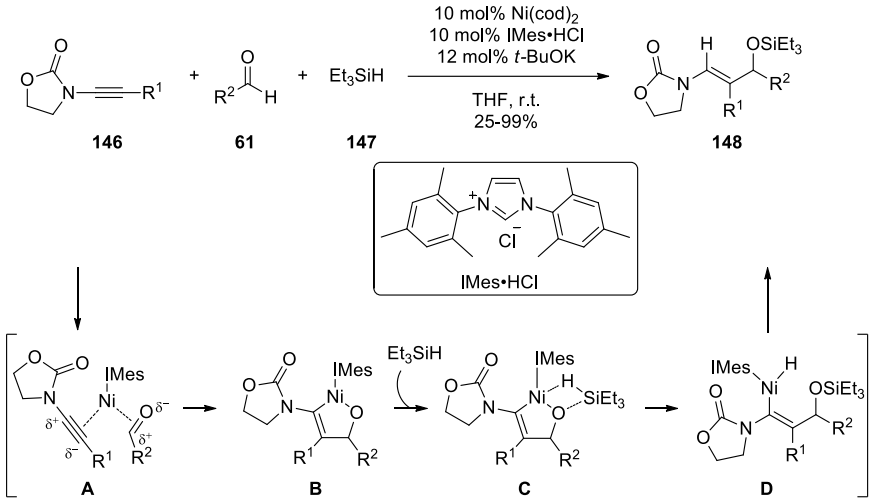
Scheme 70: Silaboration of ynamides.



Scheme 71: Suzuki-Miyaura coupling of enamide **143** with aryl iodides**.**

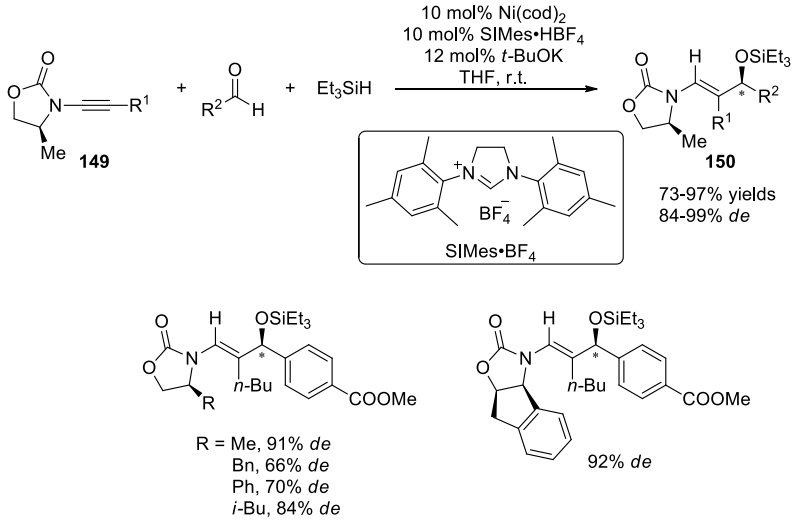
With carbon-carbon bond formation

Sato's group [81] demonstrated a nickel-catalyzed addition of oxazolidinone-derived ynamides **146**, aldehydes, and triethylsilane to construct new β-C-C bonds on ynamides (Scheme **72**). The active catalyst was Ni(0)-NHC (nitrogen heterocyclic carbene) complex, which was generated from $Ni(cod)_2$, IMes•HCl, and *t*-BuOK. The high regioselectivity was mainly attributed to the oxanickel-cyclic **B** generated from the oxidative cyclometalation of Ni center, ynamide, and aldehyde. As a result of an electronic match between ynamide and aldehyde. The cleavage of the nickel-oxygen bond by σ-bond metathesis (depicted as intermediate **C**) of the nickelacycle **B** with Et_3SiH afforded hydridenickel intermediate **D**. The reductive elimination from **D** finally produced the γ-silyloxyenamide derivatives **148**.

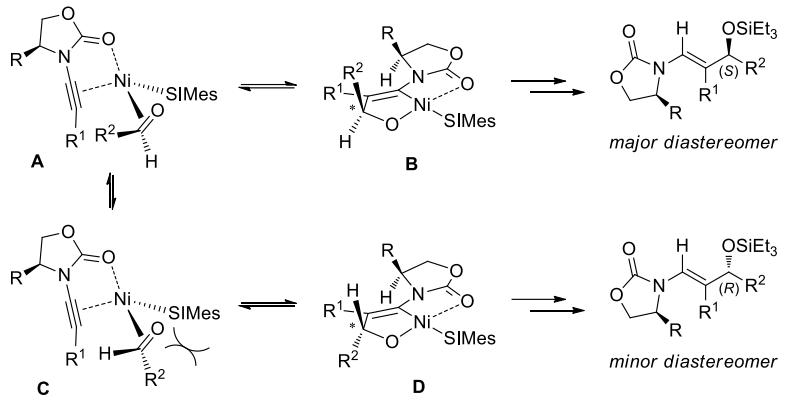


Scheme 72: Nickel-catalyzed multicomponent coupling.

Later, the authors [82] used ynamides **149** with a chiral auxiliary to achieve the asymmetric synthesis of γ-siloxyenamides **150** in high diastereoselectivity. Surprisingly, the methyl group on the oxazolidinone ring induced excellent diastereoselectivity and yield, whereas other bulky groups (*e.g.* Bn, Ph, *i*-Bu) led to a decrease of *de*% (Scheme **73**). It was proposed that due to the steric repulsion between the R^2 group in the aldehyde and the bulky SIMes ligand, nickelacycle **B** was formed preferably. However, when the chiral auxiliary became larger, the steric repulsion between R^2 and R would increase, which made the pathway through nickelacycle **D** less difficult, thus a decrease of diastereoselectivity was observed (Scheme **74**).

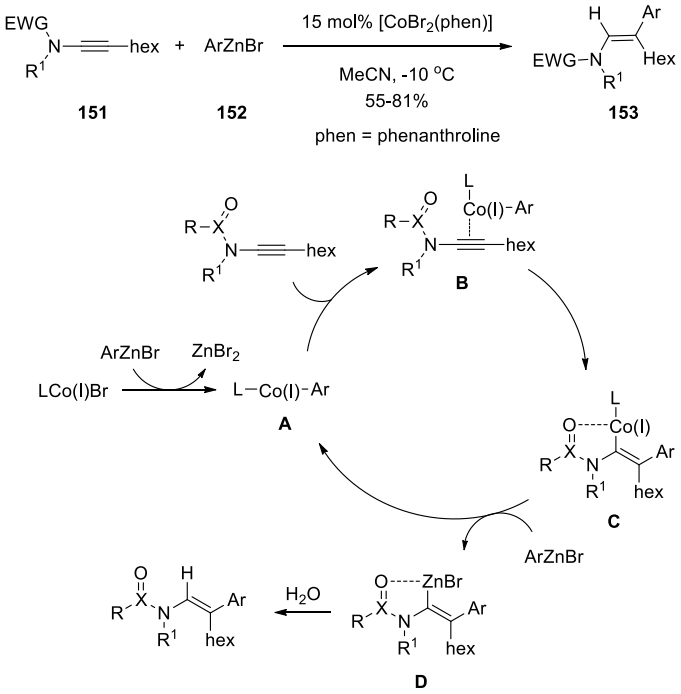


Scheme 73: Nickel-catalyzed asymmetric multicomponent coupling.



Scheme 74: Possible reason for diastereoselectivity.

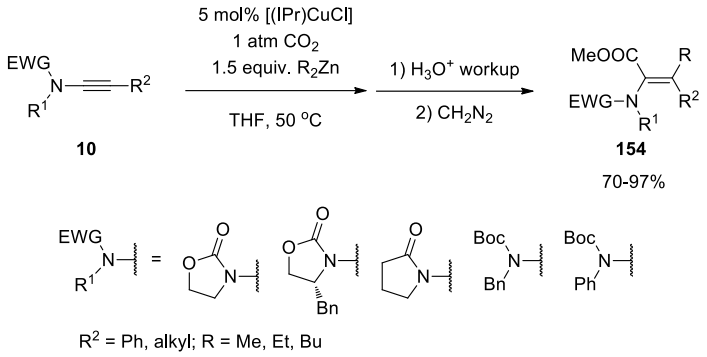
Gosmini, Gillaizeau, and co-workers [83] developed a cobalt-catalyzed hydroarylation of ynamides **10** in the presence of arylzinc derivatives **146**, providing β-aryl enamides **147** as main product in moderate to good yields (Scheme **75**). This reaction proceeded through transmetalation between organozinc and cobalt complexes, *cis*-addition to the C-C triple bond, a second transmetalation from Co to Zn, and protonation. It was assumed that the coordination between EWG and Co center favored the arylation at β-site of ynamides.



Scheme 75: Cobalt-catalyzed hydroarylation of ynamides.

Hou *et al* [84] developed a copper-catalyzed alkylative carboxylation of yanmides with CO_2 and dialkylzinc reagents. In the presence of the optimal catalyst [(IPr)CuCl], a variety of ynamides (oxazolidinone, lactam, and Boc group containing) underwent this transformation to afford the corresponding α,β-dehydroamino acid derivatives

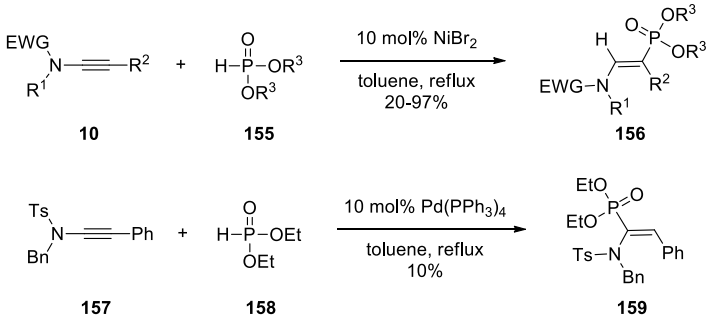
154 (Scheme **76**). This reaction would be a desirable method for the synthesis of highly substituted α,β-dehydroamino acid derivatives due to its high regioselectivity (with alkylation at β-position and carboxylation at α-position) and stereoselectivity (*cis* addition) *via* one-pot procedure.



Scheme 76: Copper-catalyzed alkylative carboxylation of ynamides.

With carbon-phosphorus bond formation

Evano, Rabasso, and co-workers [85] found that in the presence of $NiBr_2$ catalyst, the hydrophosphonylation of ynamides **10** with dialkylphosphites **155** proceeded efficiently to form β-aminovinylphosphonates **156** with *E* double bond configurations (Scheme **77**). Diphenyl phosphites were inactive however, with ynamides recovered. $Pd(PPh_3)_4$ was found to give opposite regioselectivity; the phosphonylation occurred at α-position with a poor yield (10%).

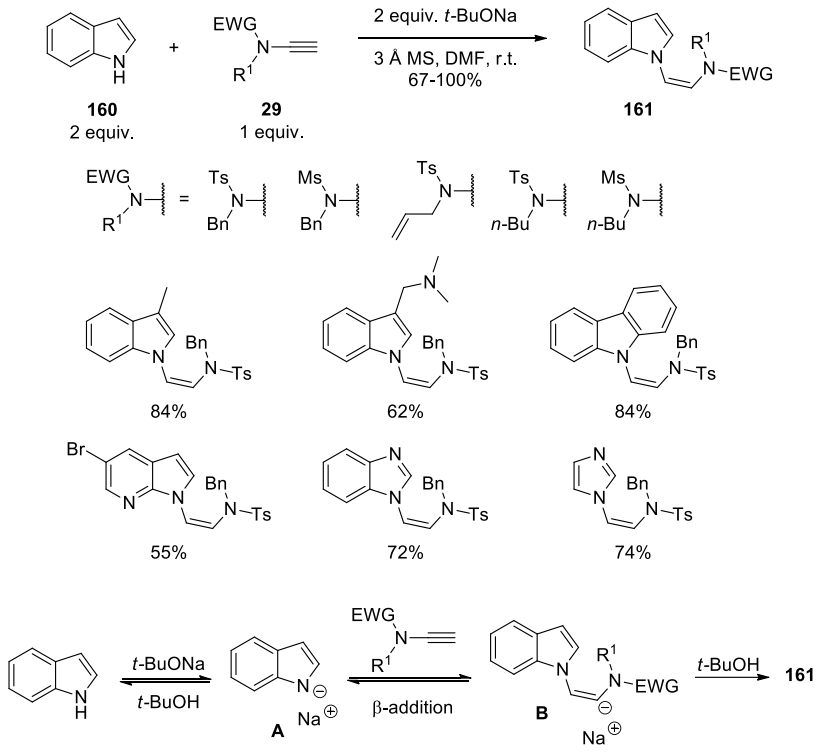


Scheme 77: Addition of dialkyl phosphates to ynamides.

With carbon-nitrogen bond formation

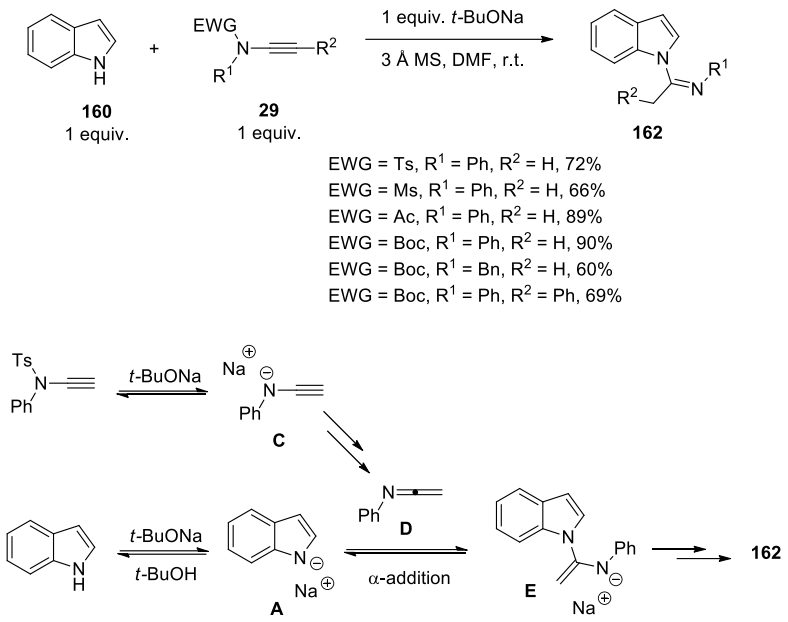
Dodd's group [86] found that the N-H bond of indole could add to terminal ynamides **29** to form *Z*-indoloetheneamides **161** without transition metal catalyst (Scheme **78**). This reaction required 2 equivalents of strong base (*t*-BuONa) and 2 equivalents of indole in order to achieve a high conversion of ynamides. Many indolic derivatives (*e.g.* skatole, gramine, carbazole, azaindole, imidazole, *etc*.) also reacted quite well. Internal ynamides did not react with indole and led to complex mixture. The addition of indole anion **A** (after deprotonation by strong base) occurred at the β-position of

the ynamide, which was rather special because nucleophilic attack commonly happened at the α-position.



Scheme 78: N functionalization of indoles with terminal ynamides.

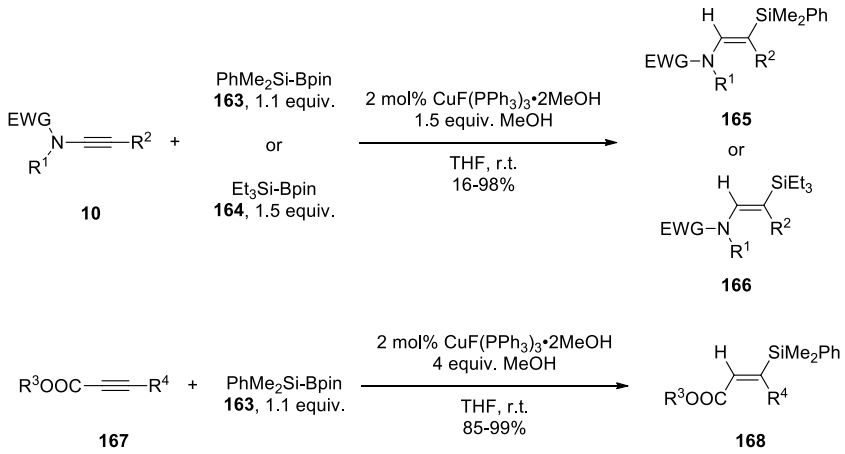
By tuning the *N*-substituents R^1 and EWG, and reducing indole and strong base to 1 equivalent, the reaction pattern changed drastically and the amidine products **162** were obtained (Scheme **79**). The sulfonamide, acetamide, and *tert*-butoxycarbamate substrates, along with *N*-phenyl substituent, all led to amidine products. The *N*-Boc and *N*-benzyl combination also worked the same. It was proposed that the strong base could cleave the EWG of those substrates to give amides **C**, which were converted to the reactive ketenimine **D** after tautomerization and protonation. Addition of indole anion **A** to the α-site of ketenimine **D** led to the amidine **162** eventually.



Scheme 79: Formation of amidine products.

With carbon-silicon bond formation

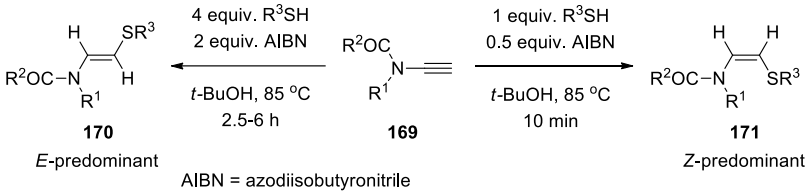
In the presence of Cu catalyst, silylboranes (*e.g.* $PhMe_2SiBpin$, $Et_3SiBpin$) could act as silylation reagent solely to do the β-silylation of ynamides instead of borylation. In the work of Riant, Evano, and co-workers [87], $CuF(PPh_3)_3$•2MeOH was screened to be the optimal catalyst. A series of ynamides **10** were converted into β-silylenamides **165** or **166** in good yields with excellent *E* stereoselectivities (Scheme **80**). The key step in the catalytic cycle was the silylcupration to the ynamide triple bond. The β-silylation was attributed to the coordination between EWG and Cu center; the single stereoisomer was attributed to the *cis*-silylcupration. Propiolates **167** also underwent silylcupration to give corresponding β-silylacrylates **168**.



Scheme 80: Silylation of ynamides and propiolates.

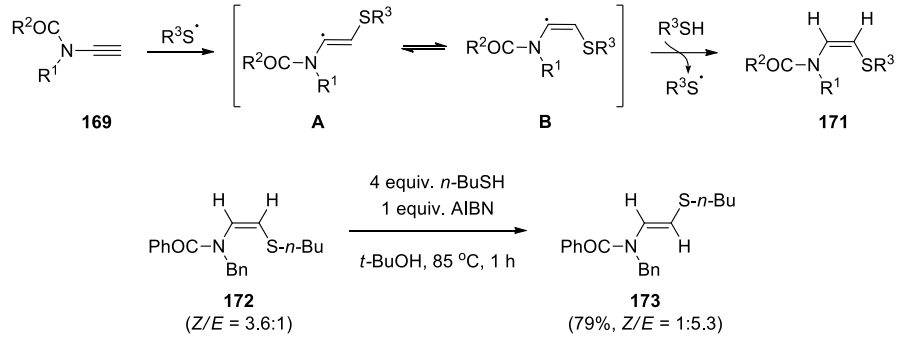
Radical process

Radicals are electron-deficient, therefore, the addition of radical species to ynamides prefers at the β-position. The addition of a thiyl radical to an ynamide would produce a β-thioenamide. Castle's group [88] reported a stereoselective addition of thiyl radicals to terminal ynamides. Both *Z*- and *E*-β-thioenamides could be obtained by varying the reaction conditions. When stoichiometric thiyl radicals (1 equivalent of thiol and 0.5 equivalent of AIBN as radical initiator) were utilized and the reaction was heated for a short time (10 min) at 85 °C in *t*-BuOH, *Z*-β-thioenamides **171** were the major product. When the reaction conditions changed to excess thiyl radicals (4 equivalents of thiol and 2 equivalents of AIBN) and longer reaction time (hours), *E* isomers **170** became the major product (Scheme **81**). PhSH and *n*-BuSH followed these two patterns. The exception was the bulky *t*-BuSH. The major product was the *Z* isomer even subjected to the *E* selective conditions.



Scheme 81: Addition of thiyl radicals to terminal ynamides.

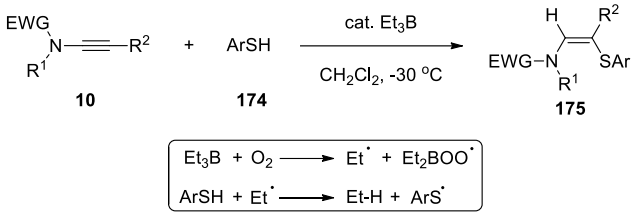
Regioselective addition of a thiyl radical to the terminal ynamide **169** provided vinyl radicals **A** and **B**, which would rapidly equilibrate. Radical **B** had less steric hindrance at the radical center. Its hydrogen abstraction from the thiol afforded the *Z*-β-thioenamide **171** as the kinetic product (Scheme **82**). Excess thiyl radical in the reaction mixture allowed the isomerization of **171** to the thermodynamically more stable *E* isomer *via* a radical addition-β-thiyl radical elimination pathway. The transformation of *Z* adduct **172** to *E* adduct **173** under thermodynamic conditions was confirmed by the control experiment.



Scheme 82: Proposed radical addition.

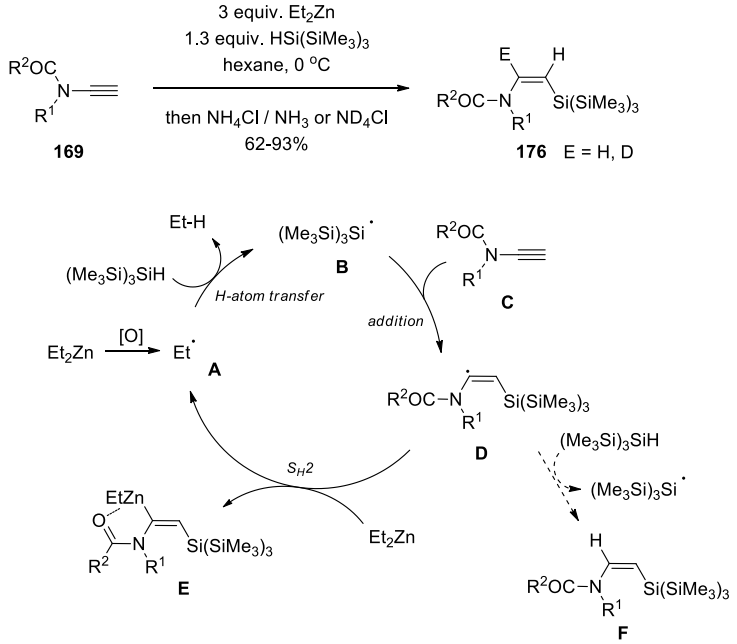
Yorimitsu, Oshima, and co-workers [89] used triethylborane (Et_3B) to initiate thiyl radicals at low-temperature (-30 °C in CH_2Cl_2). Ethyl radical, generated under oxygen, abstracted the hydrogen from arenethiols and affords the arenethiyl radicals. The

addition of these arenethiyl radicals to the β-carbon of internal ynamides **10** finally led to kinetic product, *Z*-β-thioenamides **175** (Scheme **83**).



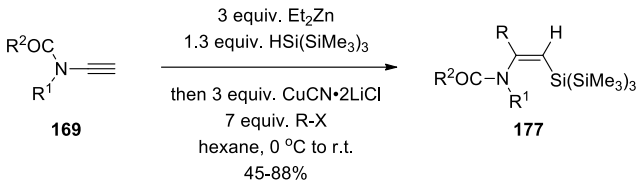
Scheme 83: Addition of arenethiols to ynamides.

Similar to diethylborane, dialkyl zinc (*e.g.* Et_2Zn), combined with hydrosilanes [*e.g.* $(Me_3Si)_3SiH$], could generate silyl radical. Oestreich, Perez-Luna, and co-workers [90] developed a *trans*-selective silylzincation of terminal yanmides through radical pathway. After quenched with NH_4Cl, *Z*-β-silylenamides **176** were obtained as the main product in good yields (Scheme **84**). The silyl radical **B** was demonstrated again to add to the β-carbon of ynamides **C** and kinetically favored vinyl radical **D** was formed. The deuterium quenching experiment showed that high percentage of deuterium was incorporated at the α-position of the product, which supported a more favorable Zn complex **E** other than the direct hydrogen abstraction from another $(Me_3Si)_3SiH$. The complex **E**, with coordination between carbonyl group and Zn center, determined the *trans* stereoselectivity of the resulting enamide.



Scheme 84: Silylzincation of ynamides and proposed mechanism.

In the presence of CuCN•2LiCl, the silylzincation intermediate could be readily coupled with organohalides to afford the corresponding α-substituted-β-silylenamides **177** (Scheme **85**).

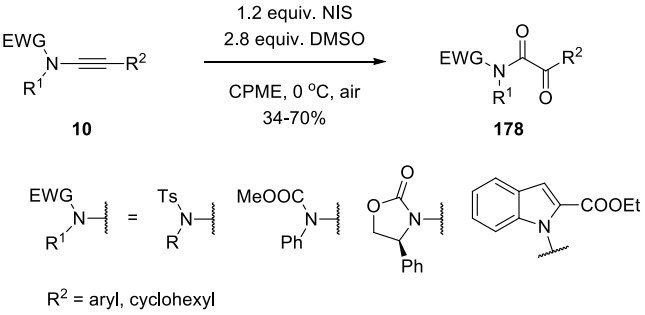


Scheme 85: Silylzincation of ynamides and copper-mediated electrophilic trapping.

Oxidation

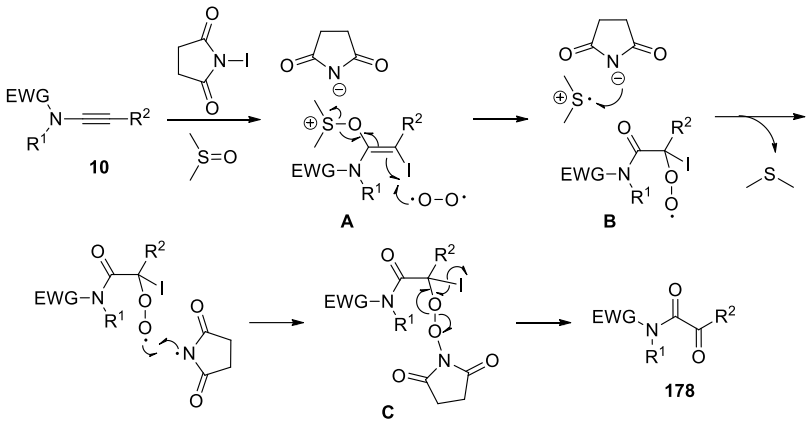
Oxidation of ynamides would generate α-ketoimide or α-ketoamide derivatives, which are biologically active moieties and versatile building blocks in organic synthesis as well. Iodine-mediated oxidation has been developed to overcome the limitations of harsh oxidative conditions and expensive and hazardous transition metals. Iwasawa's group and Zhu's group reported this oxidation in the same year.

In Iwasawa's work [91], treatment of ynamides **10** with 1.2 equivalents of NIS and 2.8 equivalents of DMSO (dimethyl sulfoxide) in CPME (cyclopentyl methyl ether) at 0 °C for 1 h generated the α-ketoimide products **178** (Scheme **86**). NIS worked as the I^+ source to initiate the oxidation, I_2 was less efficient though. DMSO (or other sulfoxides) worked as an oxygen source as the reduction product sulfane was observed. Oxygen in atmospheric air was also found to be another crucial oxidant. When the reaction was subjected to the argon, complex reaction mixture was observed.



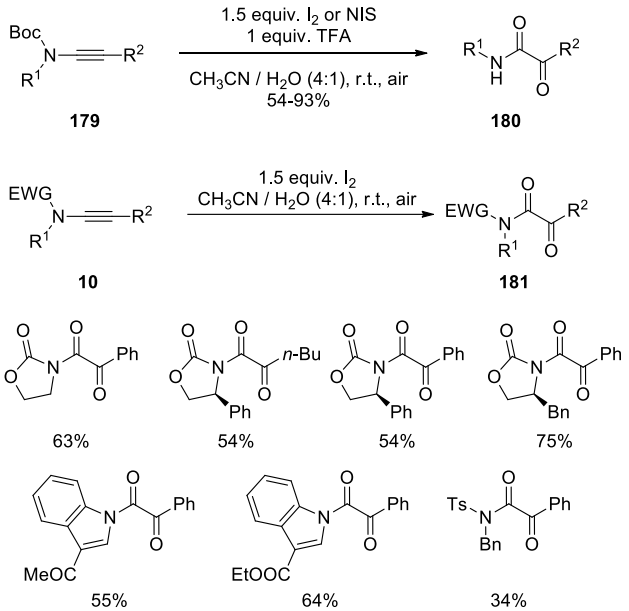
Scheme 86: Formation of α-ketoimides.

It was proposed that I^+ activated ynamide **10** to provide oxysulfonium **A**. The addition of molecular oxygen and single electron transfer formed peroxide radical **B** and thiyl radical cation. The thiyl radical cation could receive one electron from succinimide anion to convert into sulfide byproduct. Intermediate **B** was then involved with the succinimide radical and generated intermediate **C**. Cleavage through single electron transfer afforded the final α-ketoimide product **178** (Scheme **87**).

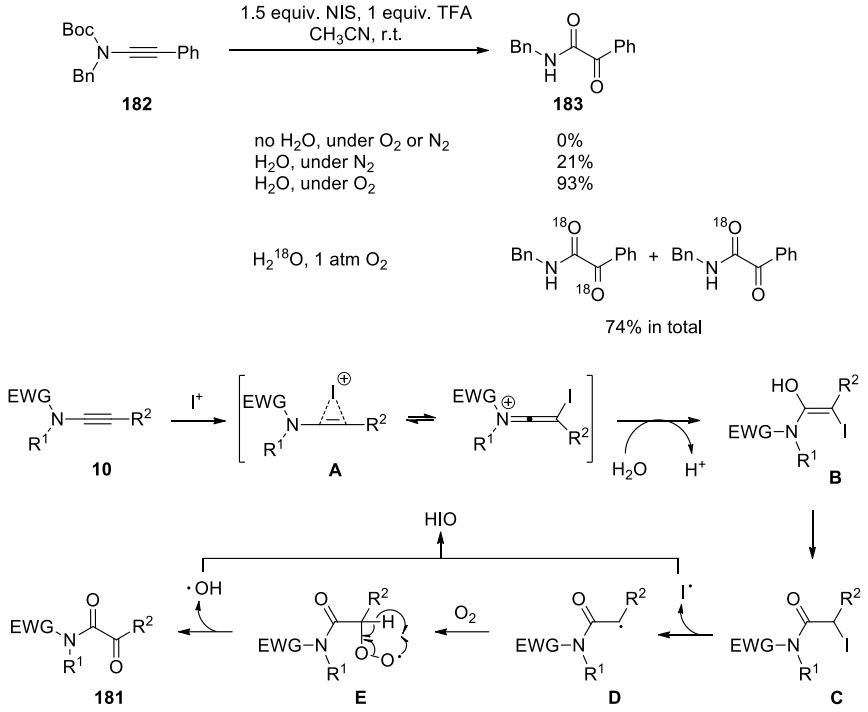


Scheme 87: Plausible reaction pathway.

In Zhu's work [92], the oxidation went well under treatment with 1.5 equivalents of NIS or I_2. The optimal solvent was a mixture of CH_3CN and H_2O. When Boc protected ynamides **179** were used as substrates, with TFA as an additive to enhance the acidic environment, Boc-deprotected α-ketoamides **180**, were obtained in high yields (Scheme **88**). Other ynamides **10** (containing *e.g.* oxazolidinone, indole, and sulfonyl groups) offered α-ketoimides **181** in moderate yields. Control experiments (Scheme **89**) showed that the desired oxidation product was not obtained in the absence of H_2O, as isotope experiment demonstrated ^{18}O would transfer from $H_2{}^{18}O$ to the oxidation product. The reaction yield could be enhanced when combined with molecular oxygen (from 21% to 93%).



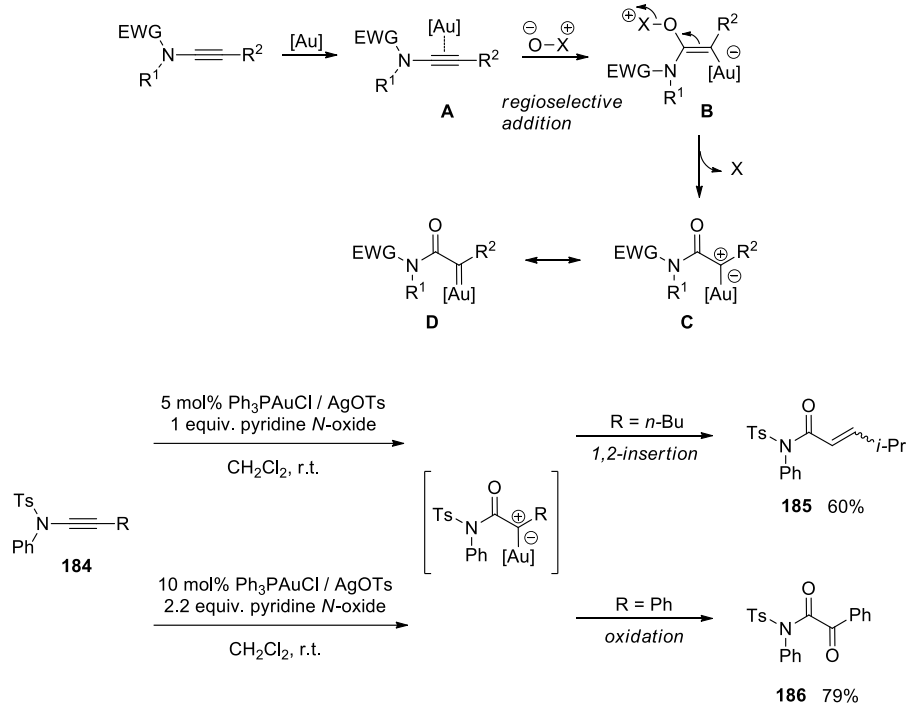
Scheme 88: Oxidation of ynamides.



Scheme 89: Control experiments and proposed mechanism.

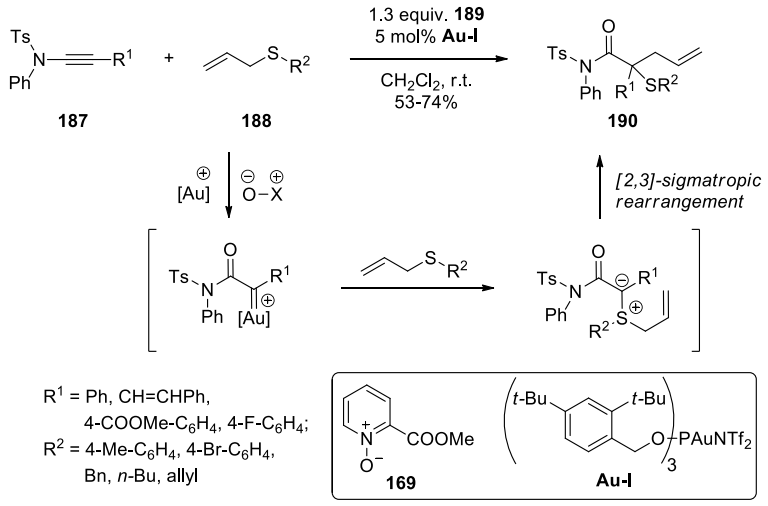
I^+ activated ynamide **A** was attacked by H_2O to form iodoenol intermediate **B** in high regioselectivity. Tautomerism gave α-iodo ketone intermediate **C**, generating radical intermediate **D** through a homolytic cleavage of the C-I bond. Radical coupling with O_2 converted **D** into peroxide radical **E**, which released a hydroxyl radical to afford α-ketoimide **181**. The hydroxyl radical might combine with the iodine radical to release HIO (Scheme **89**).

Ynamides can also be oxidized (*e.g. N*-oxides, sulfoxides, nitrones, *etc*) under transition metal catalyzed-conditions. Davies's group [93] developed a general route to synthesize α,β-unsaturated imides by a gold-catalyzed intermolecular oxidation of ynamides. The oxide underwent nucleophilic addition selectively to α site of the gold activated ynamide **A**, generating gold-carbenoid **C** or **D** (Scheme **90**). As for alkyl substituted ynamide substrates, the gold-carbenoid intermediate would undergo 1,2-insertion to provide the α,β-unsaturated imide product **185**. As for phenyl substituted ynamide substrate, double oxidation product **186** was obtained instead.



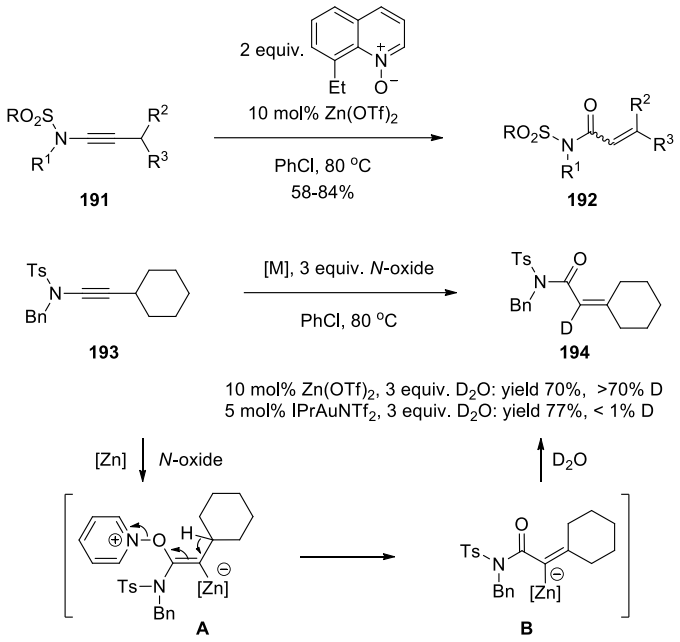
Scheme 90: Gold-catalyzed intermolecular oxidation of ynamides**.**

In light of the gold-carbenoid, Davies further coupled the chemoselective oxidation of ynamides with [2,3]-sigmatropic rearrangements of allyl sulfoniumylides to achieve one-pot synthesis of functionalized tertiary thioethers [94]. Using a combination of cationic gold phosphite complex **Au-I** as the catalyst and methylpicolinate *N*-oxide **189** as the oxidant, *S*-aryl, *S*-benzyl, and *S*-alkyl allyl sulfides **188** reacted with ynamides **187** to provide imide products **170** bearing sulfur-substituted quaternary carbons in dichloromethane at room temperature (Scheme **91**). Phenyl, alkenyl, and electron deficient aryl substituted ynamides were suitable substrates.



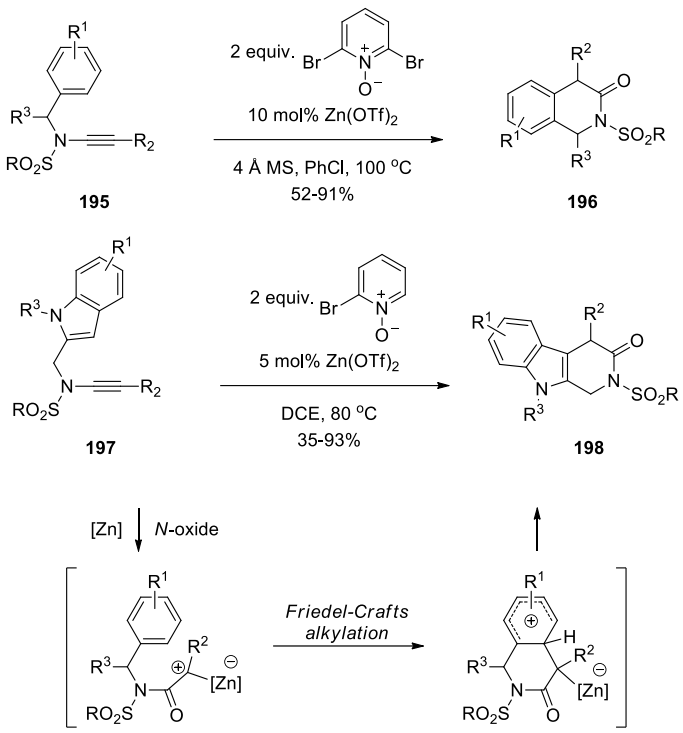
Scheme 91: Oxidation and sulfur-ylide formation sequence on ynamides.

Ye's group [95] found that *N*-sulfonylynamides **191** could also be oxidized into α,β-unsaturated imides **192** under a series of Lewis acid catalysts and *N*-oxides. The combination of 10 mol% $Zn(OTf)_2$ and 2 equivalents of 8-ethylquinoline-*N*-oxide gave the best yields (Scheme **92**). Double oxidation could be substantially suppressed. Compared to Davies' work, in which the product was formed *via* the 1,2-insertion of gold-carbenoid intermediate, this Zn-catalyzed oxidation underwent an E2-type elimination of the vinyl zinc intermediate **A** and subsequent protodemetallation of intermediate **B** to deliver the final product, which was supported by the deuterium studies. In the presence of 3 equivalents of D_2O, > 70% D was incorporated at the alkenyl position under Zn catalysis whereas almost no D was detected under Au(I) catalysis.



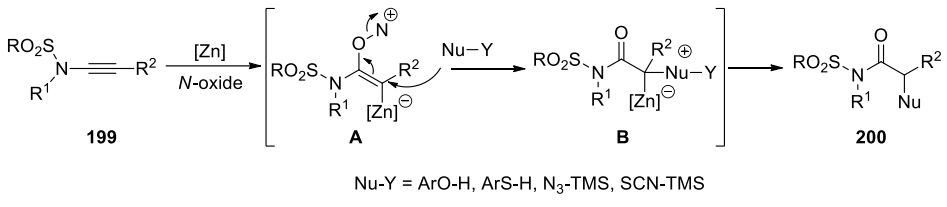
Scheme 92: Zinc-catalyzed oxidation of ynamides and plausible reaction mechanism.

When *N*-(arylmethyl)-*N*-sulfonyl ynamides **195** and *N*-(indolylmethyl)-*N*-sulfonyl ynamides **197** were subjected to the oxidation system of $Zn(OTf)_2$ and 2,6-dibromopyridine-*N*-oxide (or 2-bromopyridine-*N*-oxide), isoquinolones **196** and β-carbolines **198** were obtained in good yields, respectively, through oxidation / $C(sp^2)$-H functionalization sequence [96] (Scheme **93**). The mechanism study and the computation supported the $C(sp^2)$-H functionalization *via* an intramolecular Friedel-Crafts alkylation to arene rather than metal-carbene insertion.

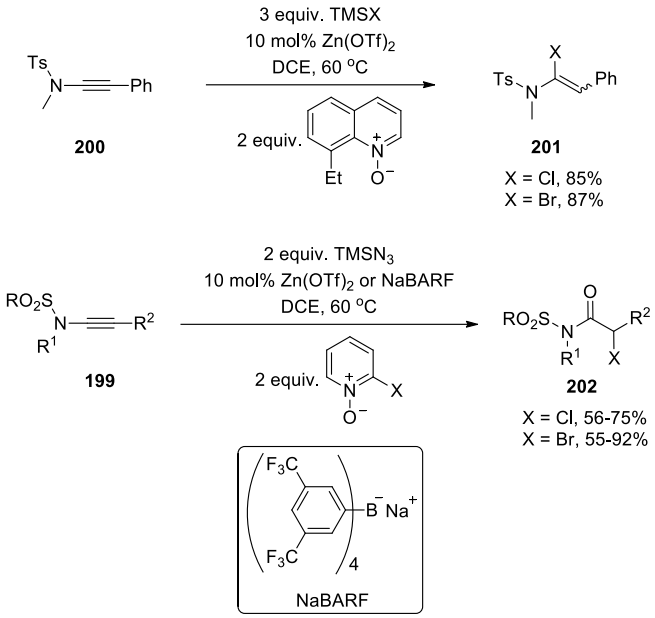


Scheme 93: Zinc-catalyzed oxidation/C-H Functionalization of ynamides.

When external nucleophiles were employed in the Zn-catalyzed oxidation system, they would attack the vinyl zinc intermediate (corresponding to the β-carbon of the ynamide) to help the cleavage of the N-O bond, which therefore led to the formation of α-functionalized imides. Ye and co-workers demonstrated that phenols, thiophenols [97], trimethylsilylazide ($TMSN_3$), and trimethylsilylisothiocyanate (TMSNCS) [98] were efficient nucleophiles to react with *N*-sulfonyl ynamides **199** under $Zn(OTf)_2$ catalyst and proper *N*-oxides to furnish α-aryloxy, α-arylthio, α-azido, α-thiocyanato imides **200**, respectively (Scheme **94**). For halogenation, TMSCl and TMSBr only led to the formation of vinyl chloride / bromide **201**. By changing the reagents to the combination of $TMSN_3$ and 2-halopyridine-*N*-oxide (halo = Cl, Br), the desired α-haloimides **202** were obtained in good yields (Scheme **95**). Noticeably, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (NaBARF) was found to be a better catalyst than $Zn(OTf)_2$ in the oxidation / bromination sequence.

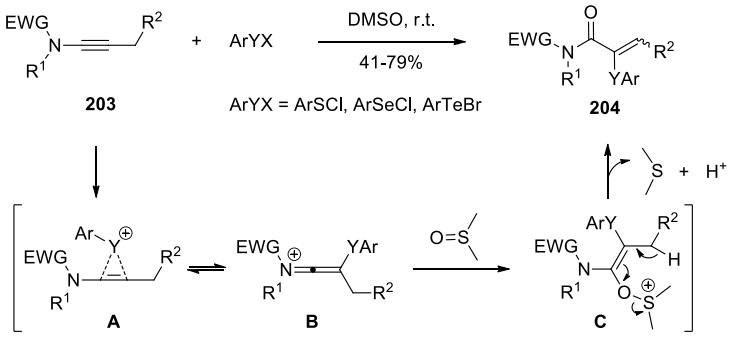


Scheme 94: Zinc-catalyzed oxidation of ynamides with nucleophiles.



Scheme 95: Oxidation / halogenation of ynamides.

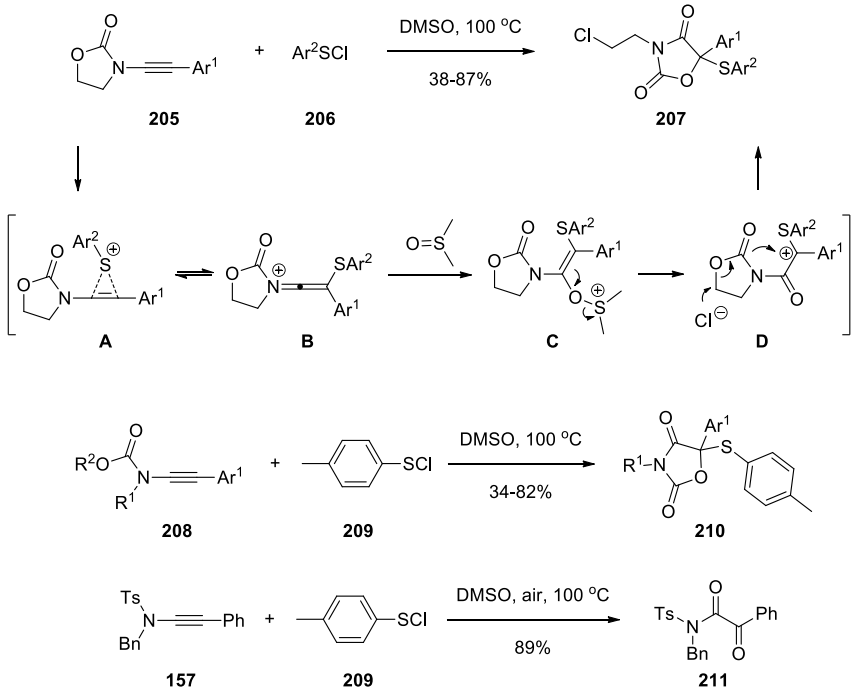
Chalcogen cations (R-S^+, R-Se^+, R-Te^+) were good electrophiles to activate alkynes. By using DMSO as the oxidant, Zhu, He, and co-workers [99] developed a chalcogen-mediated oxyfunctionalization of ynamides **203** to generate α-chalcogenyl acrylamides **204** (Scheme **96**). The chalcogen cation worked as a weak Lewis acid to activate the alkyl substituted ynamide. The resulting keteniminium **B** could be regioselectively attacked by DMSO to produce intermediate **C**. Subsequent vinyligous E2-type elimination afforded the α-chalcogenyl acrylamide.



Scheme 96: Oxyfunctionalization of ynamides.

When aryl substituted ynamides were subjected to the arenesulfenylchloride and DMSO conditions [100], there was no reaction site for the E2-type elimination after the oxothioylation. Instead, the Cl^- would open the oxazolidinone ring and the resulting carboxylic anion would attack the cation counterpart to finish a new ring closure. Therefore, the oxazolidine-2,4-dione **207** bearing sulfur-substituted quaternary carbon were obtained (Scheme **97**). For *N*-alkynyl carbamate substrates

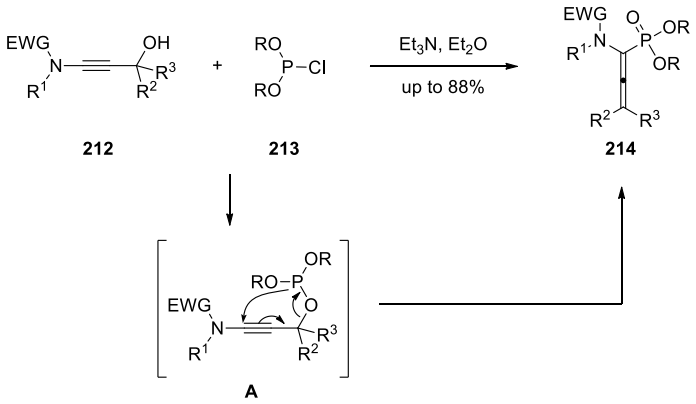
208, similar cyclization products **210** were obtained as well. However, *N*-sulfonyl ynamide **157** was transformed into α-ketoimide **211** under open air conditions.



Scheme 97: Generation of oxazolidine-2,4-diones.

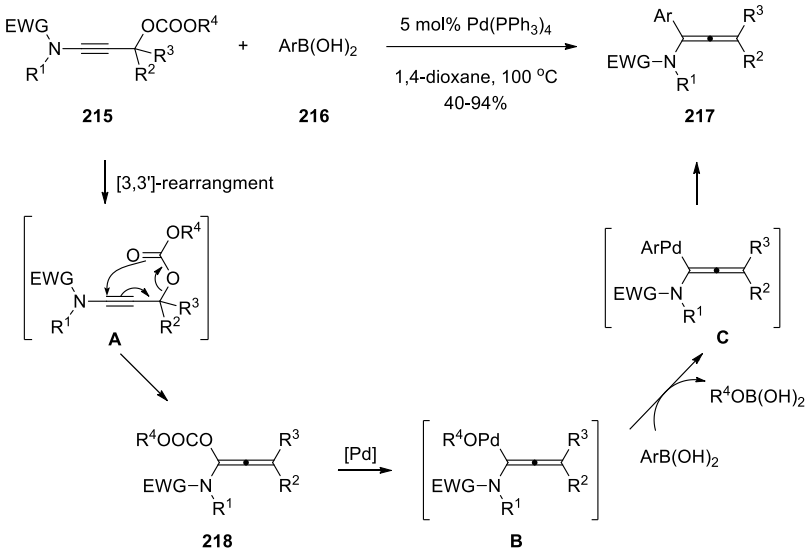
Rearrangement

The ynamide substrates with specially designed substituents can undergo rearrangement reactions to transform into interesting and useful molecules. By reacting with chlorophosphites **213**, 3-hydroxy ynamides **212** were transformed directly into allenes **214** through a [2,3]-sigmatropic rearrangement of *in situ* generated propargyl phosphite **A** [101] (Scheme **98**). This method led to the formation of a series of α-amino allenephosphonates with diverse substituents on the amine, the phosphonate, and the allene moieties.

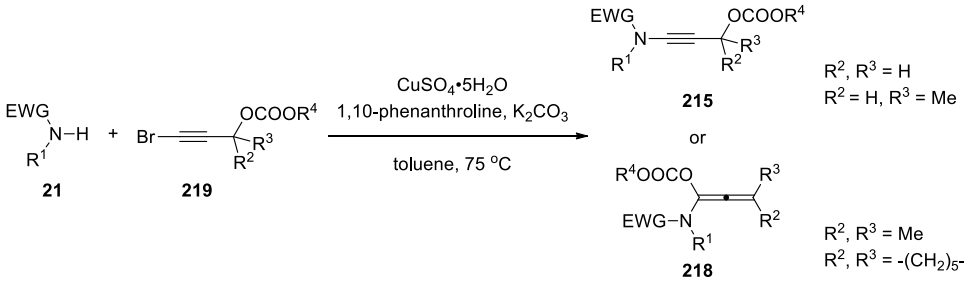


Scheme 98: Preparation of α-amino allenephosphonates.

Cao and co-workers [102] developed a method to synthesize multi-substituted allenamides **217** by Suzuki-Miyaura cross-coupling reaction between 3-alkoxycarbonyloxy ynamides **215** and arylboronic acids **216** (Scheme **99**). When subjected to Pd catalyst, 3-alkoxycarbonyloxy ynamides could undergo [3,3']-sigmatropic rearrangement to form 1-alkoxycarbonyloxy allenamides **218**, followed by which, palladium-catalyzed oxidative addition of C-O bond formed intermediate **B**, which allowed Suzuki coupling to occur at α-position. Interestingly, in the preparation of 3-alkoxycarbonyloxy ynamides **215** from amides and alkynyl bromides, when R^2 and R^3 were both alkyl groups, 1-alkoxycarbonyloxy allenamides **218** were formed instead, probably due to the high steric hindrance (Scheme **100**). They were also demonstrated to be effective substrates for the desired Suzuki-Miyaura cross-coupling reaction.



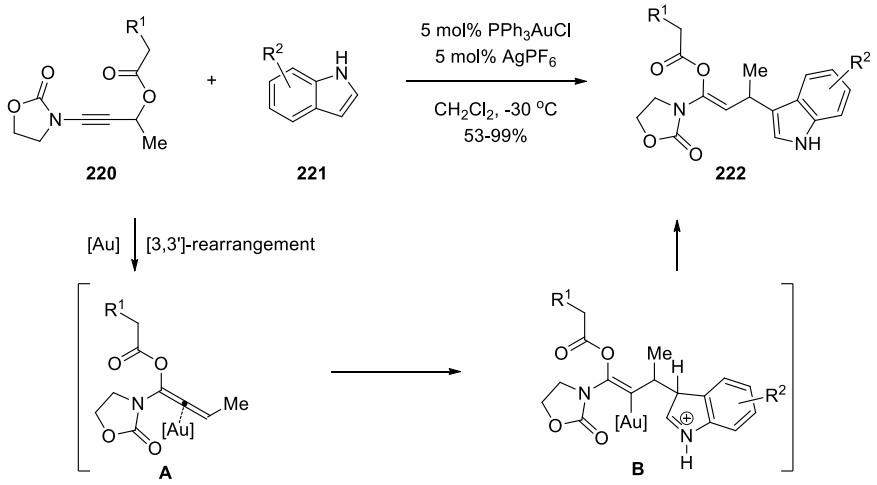
Scheme 99: Synthesis of allenamides by Suzuki-Miyaura cross-coupling reaction.



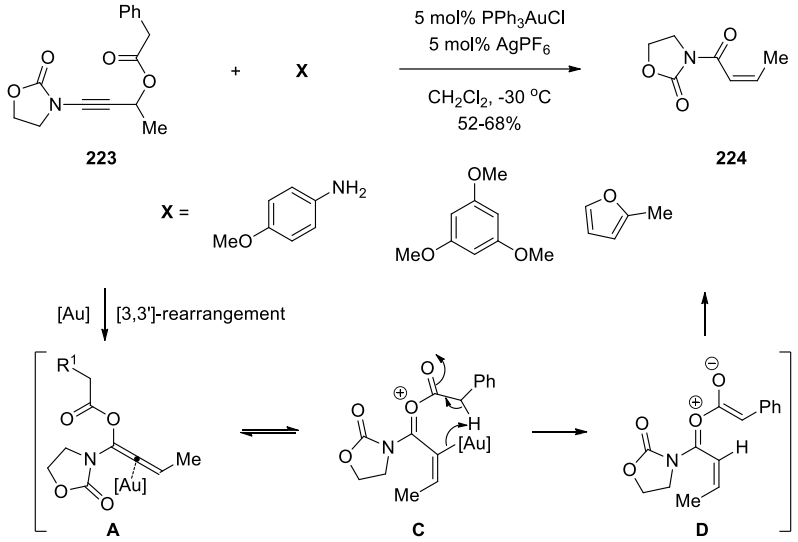
Scheme 100: Synthesis of 3- or 1-alkoxycarbonyloxy allenamides.

Similar 1,3-acyloxy migration of 3-acyloxy ynamides **220** could occur under Au(I) activation through a [3,3']-rearrangement [103]. The resulting α-acyloxyallenamide intermediate **A** smoothly reacted with indoles to form γ-indolyl α-acyloxyenamides **222** in good yields and *Z*-stereoselectivity (Scheme **101**). It was found that 4-methoxyaniline, 1,3,5-trimethoxybenzene, and 2-methylfuran were not the effective

nucleophiles as indoles, the α-acyloxyallenamide intermediate **A** actually underwent an intramolecular proto-deauration to afford enone derivatives **224** (Scheme **102**).

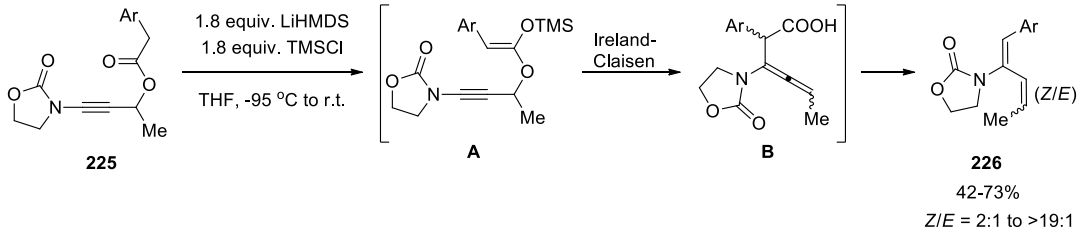


Scheme 101: Synthesis of γ-indolyl α-acyloxyenamides.



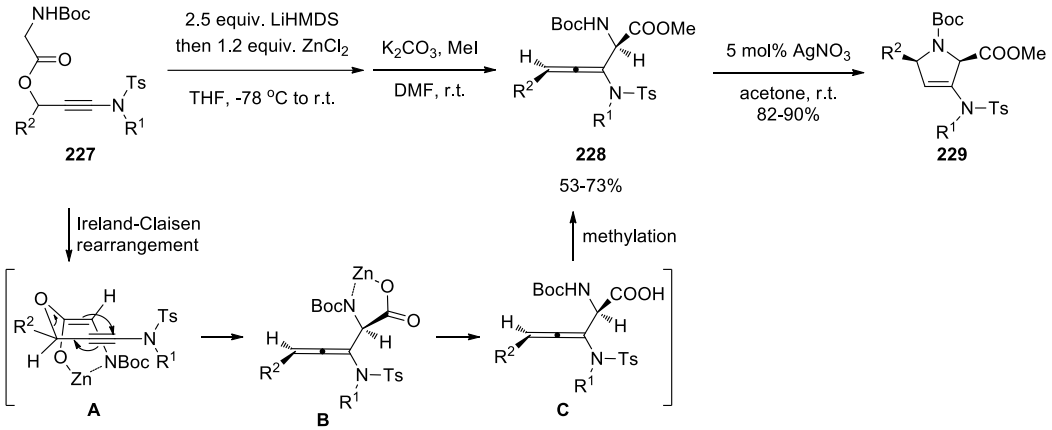
Scheme 102: Effect of other nucleophiles.

Carbery's group [104] found that when the 3-acyloxy ynamide substrates **225** were treated with LiHMDS and TMSCl, amidodienes **226** instead of allenamides were generated, which was presumably *via* an Ireland-Claisen rearrangement and subsequent decarboxylation (Scheme **103**). The methyl substituted alkene of **226** favored *Z* configuration (*Z* / *E* ratios ranging from 2:1 to > 19:1). The authors pointed out that the *Z* / *E* ratio varied on the amounts of reagents (LiHMDS, TMSCl) and the initial reaction temperature.



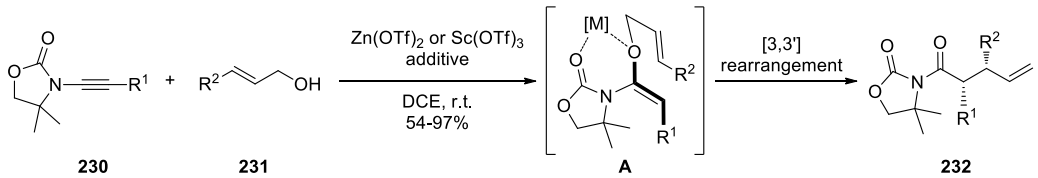
Scheme 103: Synthesis of 2-amidodienes.

N-Boc glycinates **227** derived from ynamido-alcohols could be converted into functionalized allenamides **228** in high diastereoselectivity through Ireland-Claisen rearrangement when treated with LiHMDS and $ZnCl_2$ [105] (Scheme **104**). In contrast with the previous work, these carboxylic acids were stable and the decarboxylation did not occur. After methylation of the carboxylic acid group, the functionalized allenamides could further undergo a silver catalyzed cyclization to 3-pyrrolines **239**, which were useful building blocks.



Scheme 104: Synthesis of functionalized allenamides.

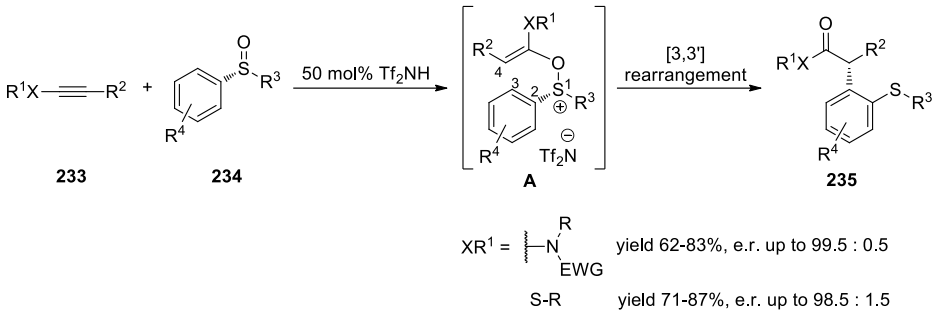
Gaunt and co-workers [106] reported the stereoselective [3,3']-rearrangement upon addition of ynamides **230** to the alcohol **231**, providing (*E*)-enolate (in favor of *syn*-isomer **232**) (Scheme **105**) [107].



Scheme 105: Catalytic addition and [3,3']-rearrangement reactions.

By using chiral sulfoxides, Maulide's group [108] developed an asymmetric redox arylation of ynamides and thioalkynes to realize an atom-economical 1,4-chirality transfer from sulfur to carbon through a sulfonium [3,3']-rearrangement (Scheme **106**).

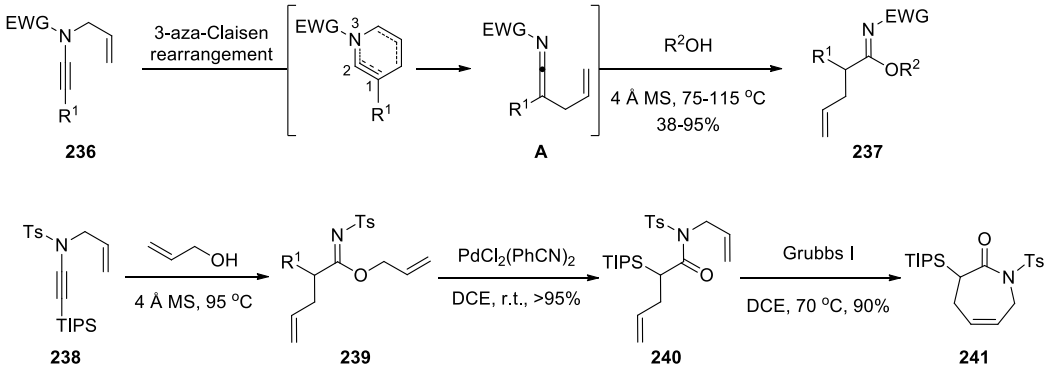
Under 50 mol% Tf_2NH, the chiral sulfoxide **234** first underwent α-addition to the ynamide **233** (or thioalkyne) and formed sulfonium intermediate **A**. The following [3,3']-sigmatropic rearrangement established the chirality (enantio ratio up to 99.5 : 0.5) at the β-position of the ynamide (or thioalkyne) and transferred the oxygen atom to the α-position spontaneously, which efficiently gave access to chiral arylated amides and thioesters **235**.



Scheme 106: Asymmetric redox arylation.

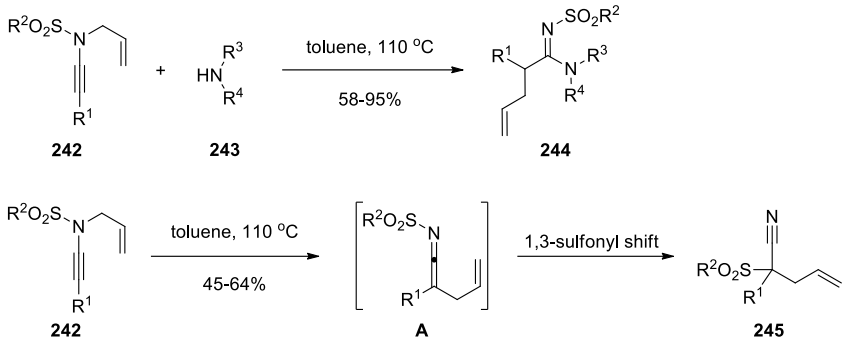
N-Allyl ynamides were discovered to rearrange to allyl substituted ketenimines through thermal aza-Clainsen rearrangement or Pd-catalyzed allyl transfer. Hsung and co-workers showcased a series of novel chemistry based on this know-how.

The ketenimine intermediate could be trapped by alcohols and transformed into *de novo* imidates [109]. After condition screening, the authors found that heating of *N*-allyl ynamides **236** in alcoholic solvents in the presence of 4 Å molecular sieves led to imidates **237** in moderate to excellent yields (Scheme **107**). Especially, when allyl alcohol was used, the resulting diallyl imidate **239** could further undergo a [3,3']-rearrangement in the presence of catalytic $PdCl_2(PhCN)_2$ and subsequent ring-closing metathesis to afford seven-member ring product azapine-2-one **241**.



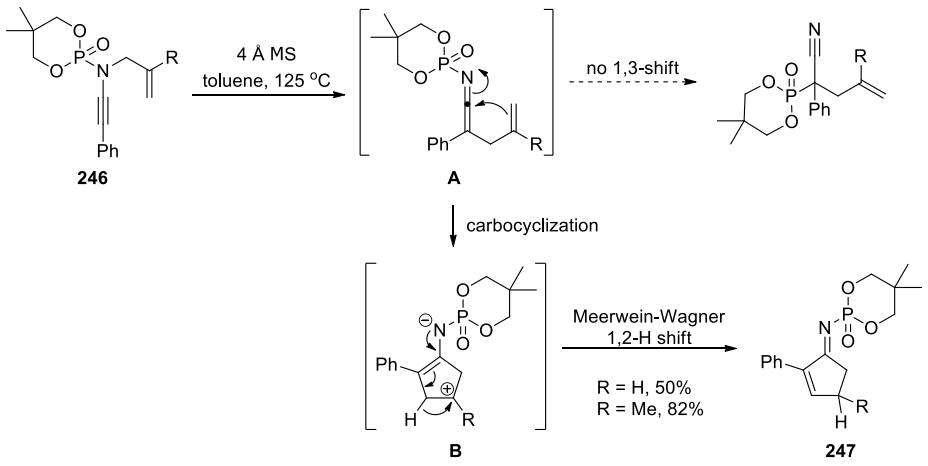
Scheme 107: Aza-Claisen rearrangements of *N*-allyl ynamides.

Similarly, simple heating of *N*-allyl ynamides **242** and amines **243** in toluene at 110 °C afforded amidines **244** in good yields [110] (Scheme **108**). When there was no nucleophile in the reaction, a 1,3-sulfonyl shift from N to C took place after the aza-Claisen rearrangement of *N*-allyl ynamides **242**, which led to tertiary nitriles **245**.

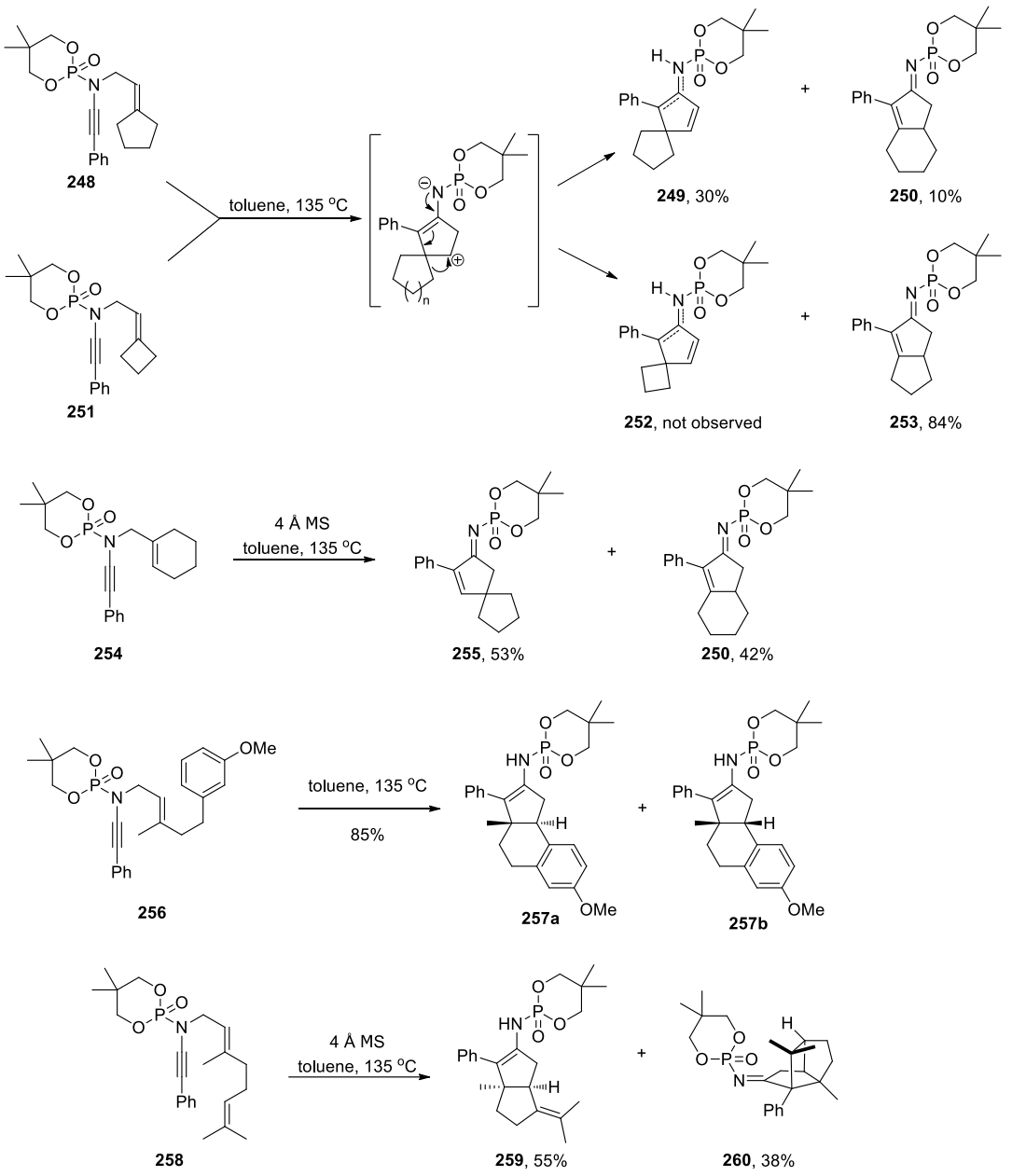


Scheme 108: Aza-Claisen rearrangement and 1,3-sulfonyl shift.

When *N*-allyl-*N*-phosphoryl ynamides **246** were the substrates, the 1,3-phosphoryl shift of allyl ketenimines **A** did not occur. Instead, a carbocyclization of allyl ketenimines **A** took place to form intermediate **B**, which underwent Meerwein-Wagner 1,2-hydride migration to provide 5-member cyclic products **247** [111] (Scheme **109**). With functionalized allyl moieties, such as 4 to 6-member rings, electron-rich arene and terpenes, various bi- and tricyclic scaffolds were afforded (Scheme **110**). Regarding **248** bearing an exocyclic alkene, upon en-ynamide cyclization, the Meerwein-Wagner-type alkyl migration proceeded to deliver ring-expanded product **250** due to the spirocyclic strain, alongside with a hydride migrated **249**. When a highly strained 4-membered ring was introduced (**251**), the alkyl migration was dominated, giving ring-expanded **253** as the sole product. As for **254** with the cyclic alkene, a ring-contracted **255** was afforded through the Meerwein-Wagner-typed alkyl migration, together with the hydride migrated **250**. Followed by this, the *p*-methoxyphenyl group in **256** and the dimethyl alkene in **258** served as nucleophiles to undergo Prins-type cyclization, which contributed to tricyclic and bicyclic products.



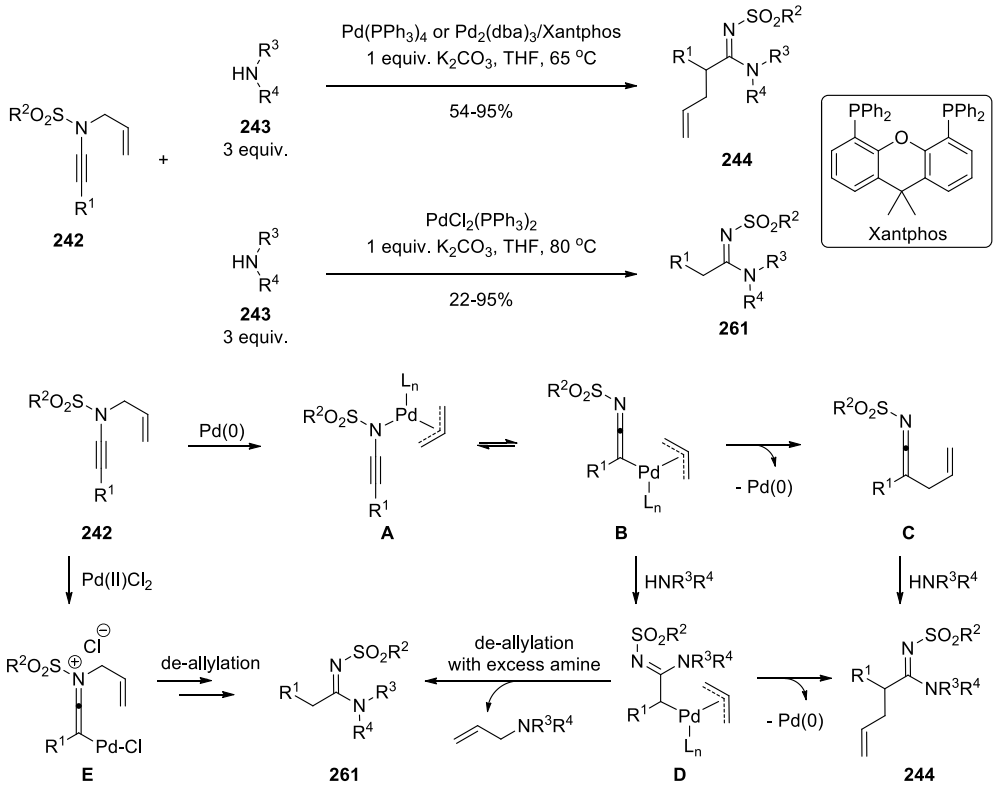
Scheme 109: Cascade carbocyclization of *N*-allyl-*N*-phosphoryl ynamides.



Scheme 110: Cascade carbocyclization of *N*-allyl-*N*-phosphoryl ynamides.

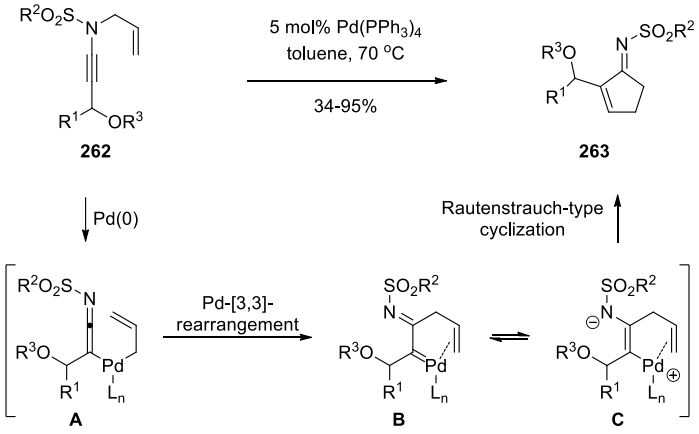
The rearrangement of *N*-allyl ynamides catalyzed by palladium experienced a different pathway from the thermal aza-Claisen rearrangement (Scheme **111**). The *N*-allyl ynamide **242** would undergo an oxidative addition to the Pd(0) catalyst, which led to ynamido-π-allyl complex **A** and ketenimino-π-allyl complex **B**. The subsequent formation of amidine **244** would occur in the presence of an amine either through the trapping of ketenimine **C**, which was derived from **B** *via* reductive elimination, or through complex **D**, which was a result of the amine addition to **B** prior to the reductive elimination. When the Pd(II) catalyst was used, for example, $PdCl_2(PPh_3)_2$, $PdCl_2$, and $Pd(OAc)_2$, the deallylative amidine **261** was formed as the major product. This deallylation could occur through excessive amine nucleophilic addition to keteniminium **B** and releasing allyl amine as byproduct. It could also be envisioned

from keteniminium intermediate **E** generated from *N*-allyl ynamide with the Pd(II) speices serving as a π-Lewis acid.



Scheme 111: Palladium-catalyzed Amidine formation .

When there was no amine or other external nucleophile, *N*-allyl-*N*-sulfonyl ynamides **262** were transformed into α,β-unsaturated cyclopentenimines **263** [112] (Scheme **112**) *via* Rautenstrauch-type cyclization of **B** or **C** [112,113].



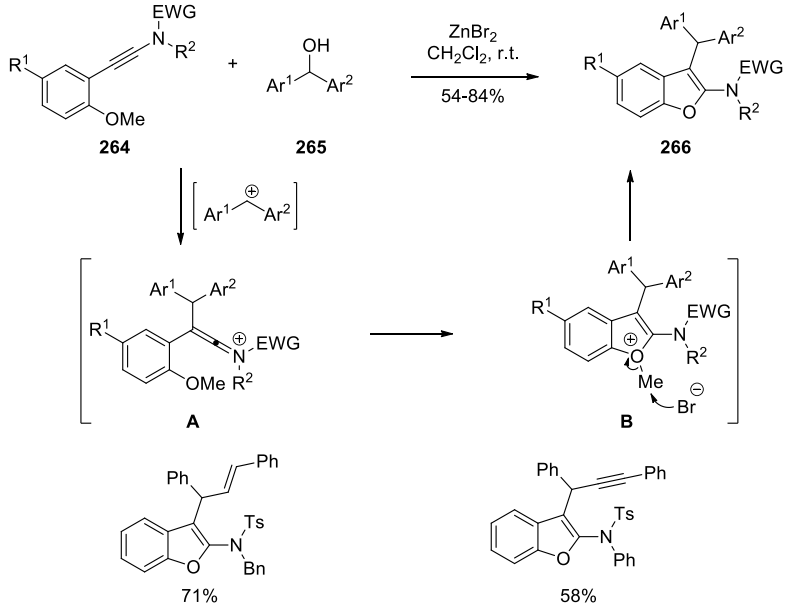
Scheme 112: Palladium-catalyzed carbocyclization of *N*-allyl ynamides.

Cyclization

Ynamides are becoming more and more attractive in rapid synthesis of cyclic and polycyclic structures [114] that can be found in natural products and molecules of biological and medicinal interest.

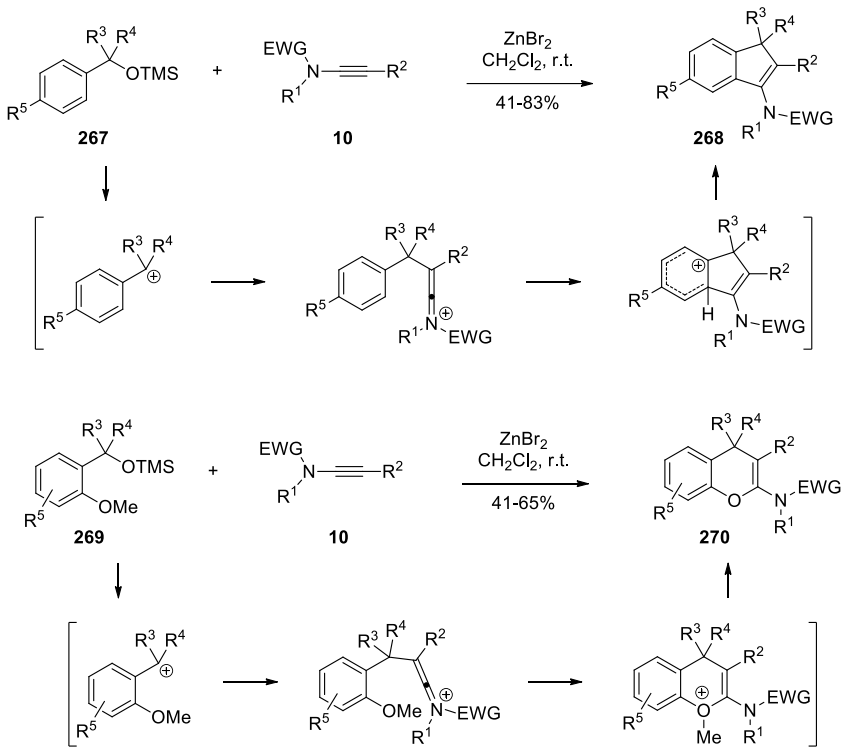
Metal-free or Lewis acid mediated cyclization

Carbocations, generated from diarylmethanol **265** and Lewis acid $ZnBr_2$, initiated an electrophilic cyclization of *o*-anisole substituted ynamides **264** to 3-alkyl-2-amidobenzofurans **266** in good yields [115] (Scheme **113**). 1-Arylprop-2-en-1-ol and 1-arylprop-2-yn-1-ol also worked as effective carbocation precursors in this transformation.



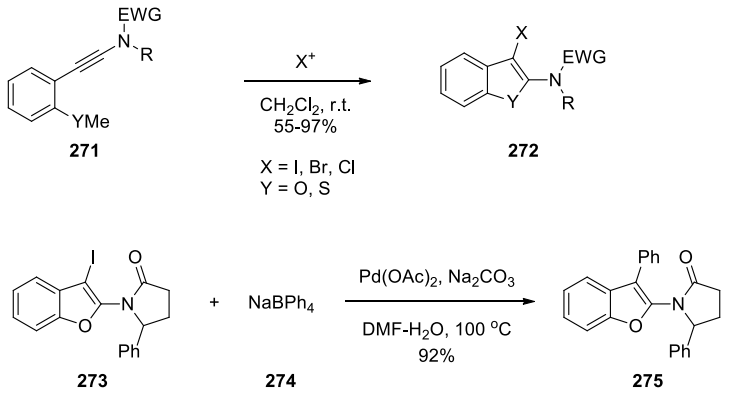
Scheme 113: Cyclization of ynamides with carbocations.

Benzyl silyl ether **267** could also be used to generate an electrophile - the benzyl carbocation with $ZnBr_2$ for an electrophilic addition of the ynamide **10**. Subsequent intramolecular Friedel-Crafts alkylation led to 1-amidoindene **268** [116] (Scheme **114**). In the case of *o*-methoxybenzyl silyl ether **269**, cyclization occurred to give 2-amido-4*H*-chromene **270** as the final product.



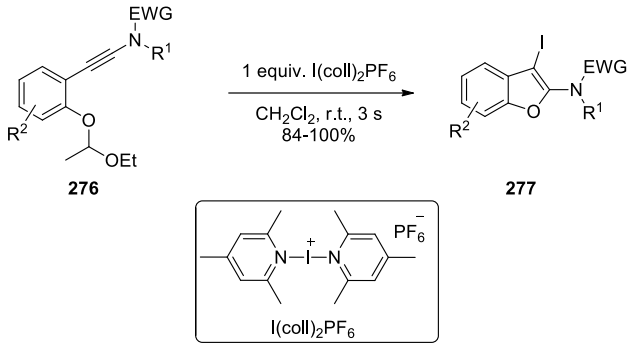
Scheme 114: Synthesis of 1-amidoindenes and 2-amido-*H*-chromenes.

Halogen cations, from I_2, NIS, NBS, and NCS, were able to activate *o*-anisole- and *o*-thioanisole-substituted ynamides **271**, and transform these substrates into 3-halogenated-2-amidobenzofurans or 3-halogenated-2-amidobenzothiophenes **272**, respectively [117] (Scheme **115**). Further Pd-catalyzed cross-coupling reactions could functionalize 3-position of the heterocycle **273**.



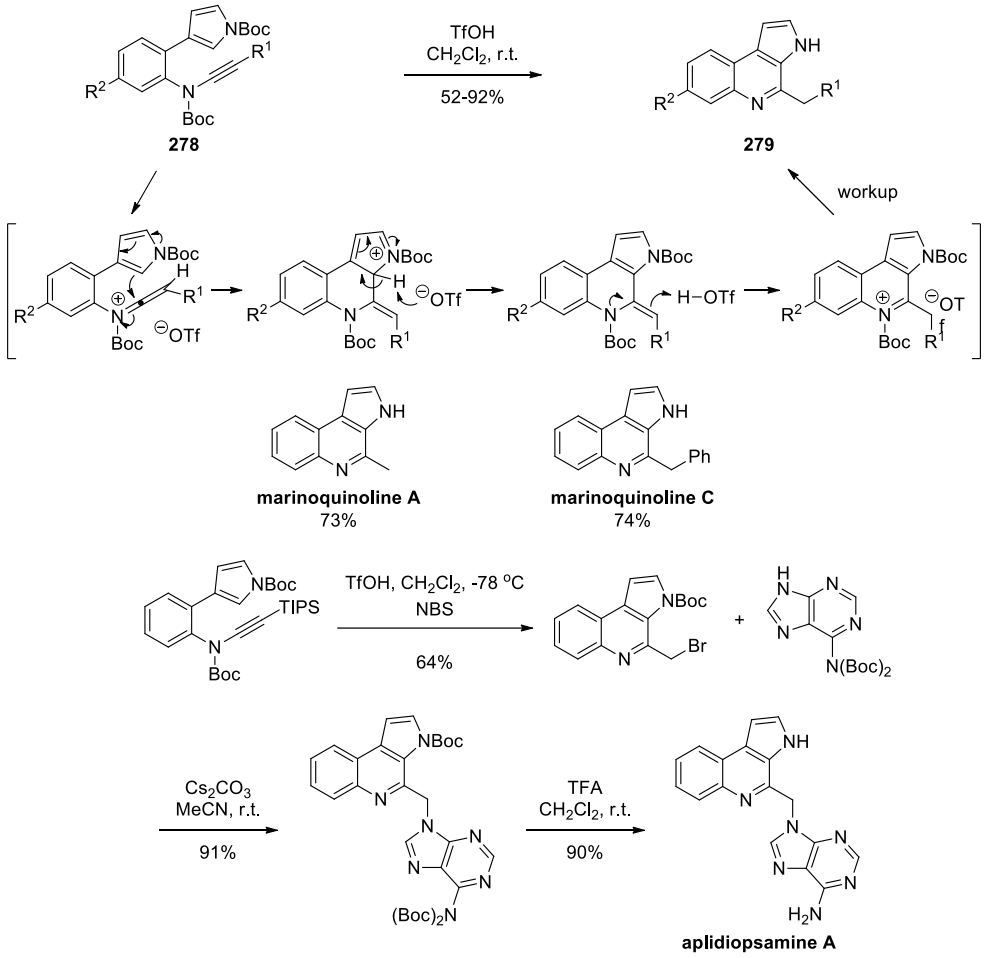
Scheme 115: Synthesis of 2-amidobenzofurans and 2-amidobenzothiophenes.

Okitsu's group [118] reported a similar iodocyclization of ynamides **276** to 3-iodo-2-amidobenzofurans **277** (Scheme **116**). By appropriately choosing ethoxyethyl ether as the leaving group on the ynamide substrates and bis(2,4,6-collidine)iodonium hexafluorophosphate [$I(coll)_2PF_6$] as the iodonium reagent, this cyclization could complete in several seconds.



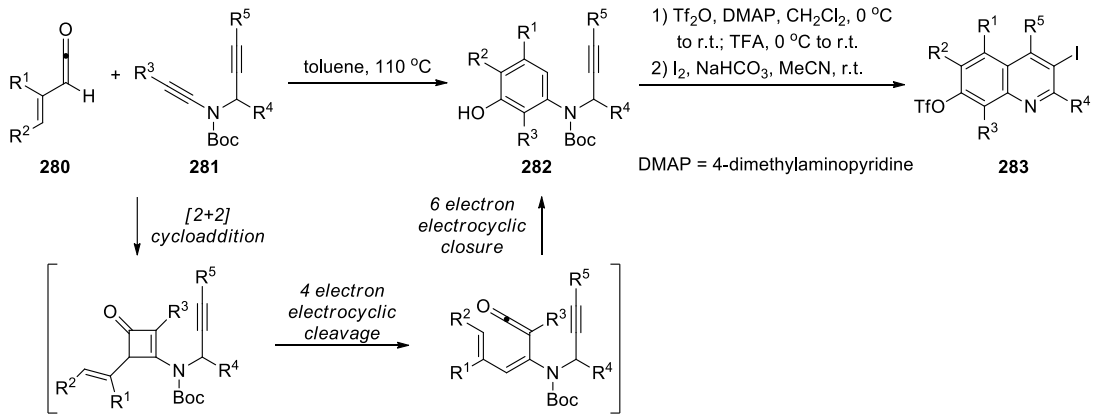
Scheme 116: Iodocyclization of ynamides.

When the specially designed *N*-aryl ynamides **278** was subjected to Brønsted acid, an electrophilic aromatic substitution would occur from the reactive keteniminium intermediate to give arene-fused quinolines **279** in good yields [119]. Yamaoka, Takasu and co-workers further demonstrated this arene-ynamide cyclization enabled facile access to natural products, for example, marinoquinolines A and C and aplidiopsamine A (Scheme **117**).



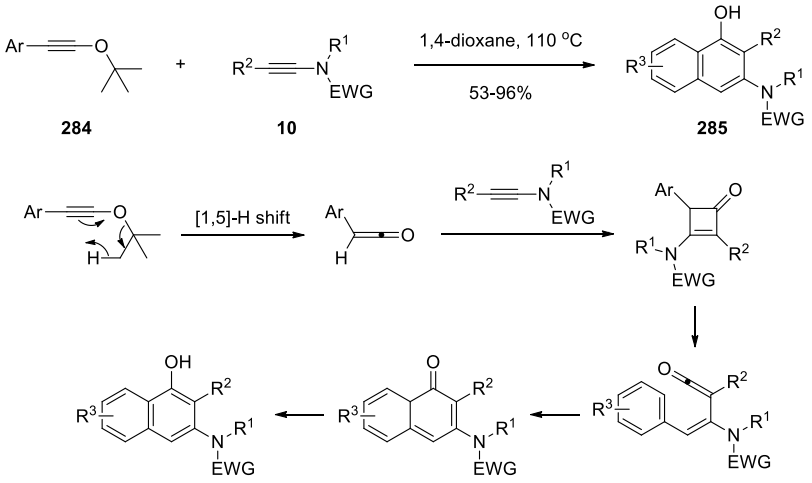
Scheme 117: Brønsted acid-promoted arene-ynamide cyclization.

To synthesize highly substituted quinolines, a tandem ynamide benzannulation / iodocyclization strategy was developed by Danheiser's group [120]. The benzannulation based on the reaction of vinylketenes **280** (*in situ* generated from cyclobutenones or diazo ketones) and *N*-propargyl-substituted ynamides **281** proceededed *via* [2+2] cycloaddition, 4-electron electrocyclic ring opening, and 6-electron electrocyclic ring closure. In the second stage of the tandem strategy, after treatment with triflic anhydride (Tf_2O), the resulting triflate derivatives further underwent iodine promoted cyclization to form quinoline products **283** (Scheme **118**).



Scheme 118: Synthesis of highly substituted quinolines.

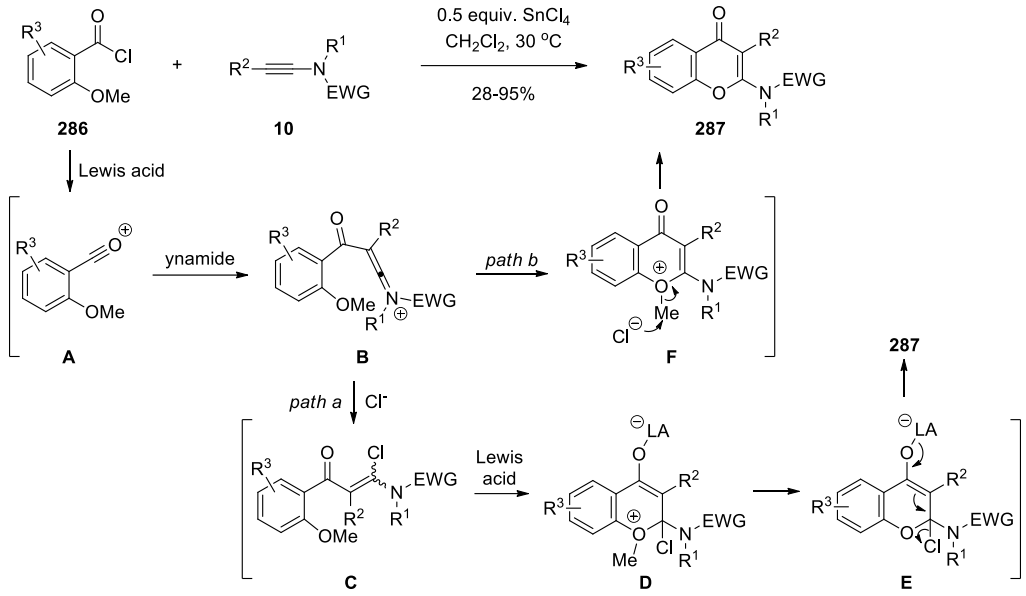
Aryl *t*-butyl ynol ethers **284** were also found to be convenient precursors to generate ketenes under heating conditions. The arylketenes, resulted from an intramolecular [1,5]-hydrogen shift of **284**, react with ynamides **10** *via* [2+2] cycloaddition-retrocyclzation (CA-RE), Friedel-Craft acylation and aromatization to afford 3-amino-1-naphthols **285** in good yields [121] (Scheme **119**).



Scheme 119: Synthesis of 3-amino-1-naphthols.

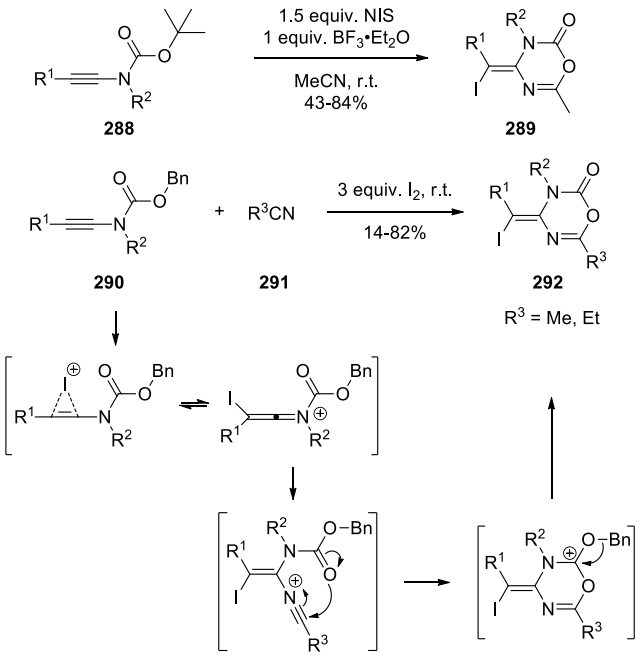
Wang, Chang, and co-workers developed a Sn(IV)-promoted annulation reaction of ynamides **10** with 2-methoxyaroyl chlorides **286** to synthesize 3-substituted

2-aminochromones **287** in mild conditions [122] (Scheme **120**). The reaction was proposed to undergo a tandem Friedel-Crafts acylation / oxo-Michael addition / demethylation / dechlorination pathway to furnish the final product, as the intermediate **C** in this pathway was isolated from the reaction. The authors also mentioned that path b through a cyclization of intermediate **B** and demethylation was also possible.



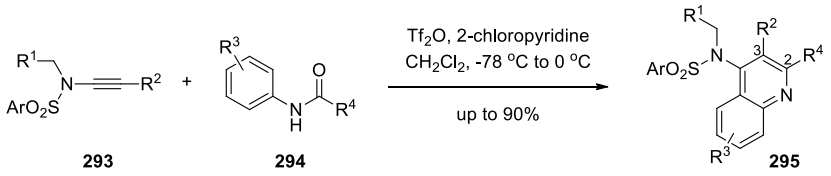
Scheme 120: Synthesis of 3-substituted 2-aminochromones.

Under the iodonium activation, *N*-alkynyl *tert*-butyloxycarbamates **288** [123] and *N*-alkynyl benzyloxycarbamates **290** [124] could accept the nucleophilic attack of acetonitrile (or propiononitrile) and further underwent a 6-*endo-dig* cyclization to offer iodine-substituted 1,3,5-oxadizazin-2-ones **289** and **292**, respectively (Scheme **121**).



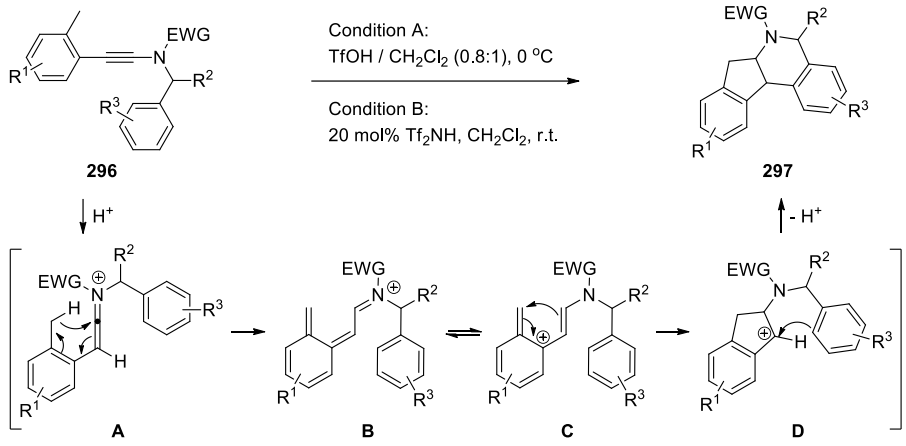
Scheme 121: Synthesis of 1,3,5-oxadiazin-2-ones.

Bräse's group [125] reported a one-pot procedure to synthesize polysubstituted 4-aminoquinolines **295** from sulfonyl ynamides **293** and electrophilically activated amides (a combination of amides **294**, triflic anhydride, and 2-chloropyridine) (Scheme **122**). This approach provided full flexibility of substitution at the C2 and C3 positions, which would be valuable from a pharmaceutical point of view.

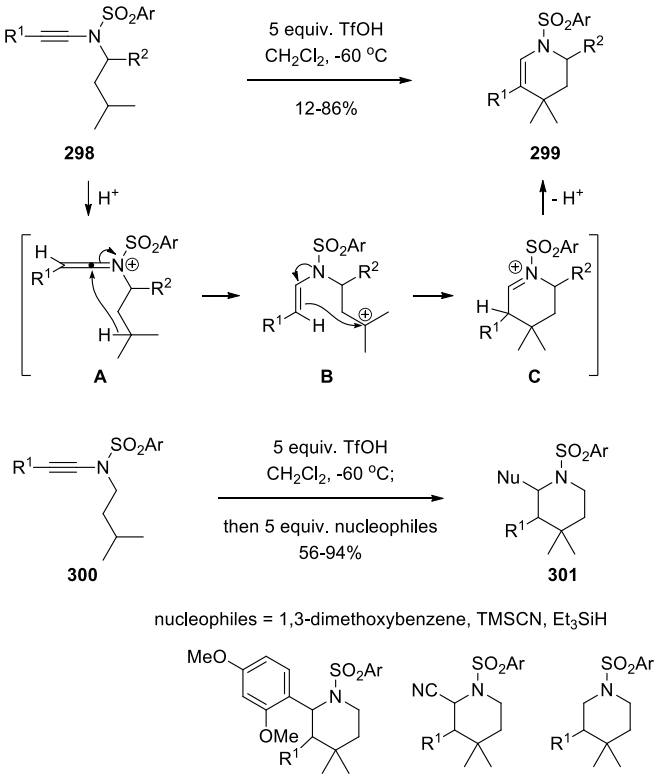


Scheme 122: Synthesis of highly functionalized 4-aminoquinolines.

Evano's group [126] found that the keteniminium ions, generated from the Brønsted acid activated ynamides **296**, were able to initiate a [1,5]-sigmatropic hydrogen shift from an unactivated benzylic position, and then a cationic polycyclization was triggered to give polysubstituted indenotetrahydroisoquinolines **297** as final products (Scheme **123**). Further investigation showed that the keteniminium ions were also able to initiate the [1,5]-hydride shift when from a properly placed isopentyl chain, and after the cationic cyclization, functionalized tetrahydropyridines **299** were formed [127] (Scheme **124**). Functionalized piperidines **301** could be readily prepared when nucleophiles (1,3-dimethoxybenzene, TMSCN, and Et_3SiH) were introduced in the reaction.

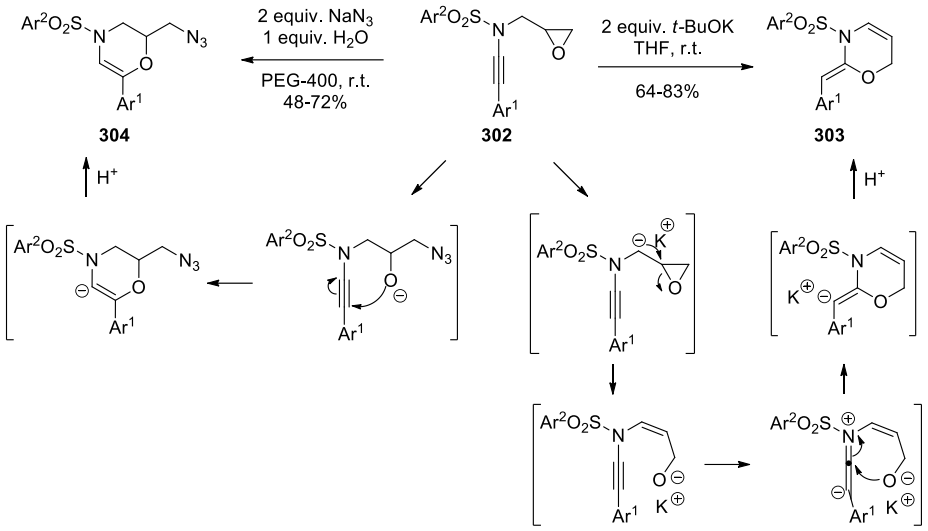


Scheme 123: Synthesis of polysubstituted indenotetrahydroisoquinolines.



Scheme 124: Synthesis of tetrahydropyridines and piperidines.

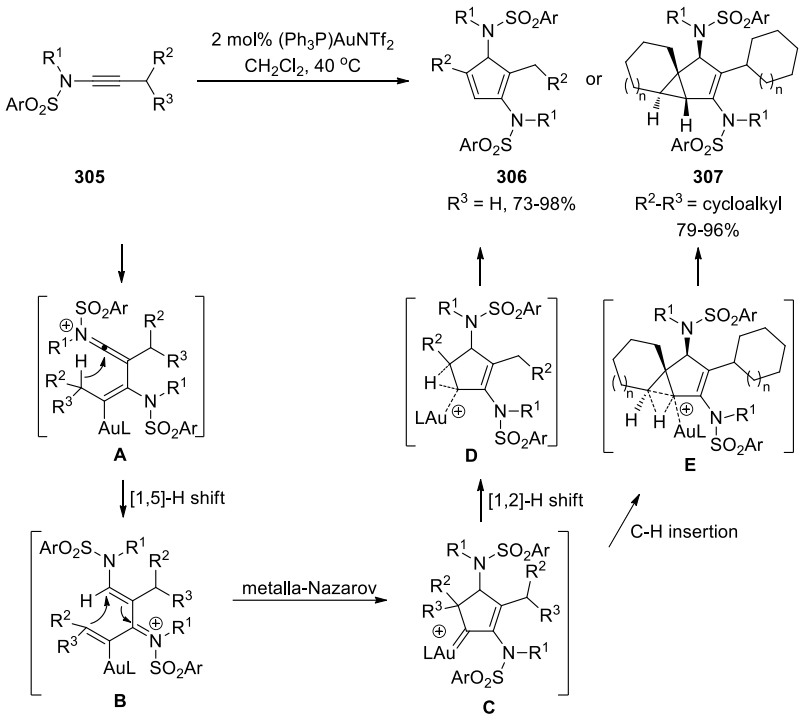
Ynamides attached with epoxides were versatile synthons [128]. When treated with strong base *t*-BuOK, the ynamide substrates **302** underwent a 6-*exo*-*dig* cyclization to become 1,3-oxazines **303** in good yields with excellent *E* stereoselectivity of the resulting C-C double bond. When treated with sodium azide NaN_3, the epoxide ring would open from the less hindered site after the nucleophilic attack of N_3^-, which triggered a different 6-*endo*-*dig* cyclization and led to 1,4-oxazines **304** as final products (Scheme **125**).



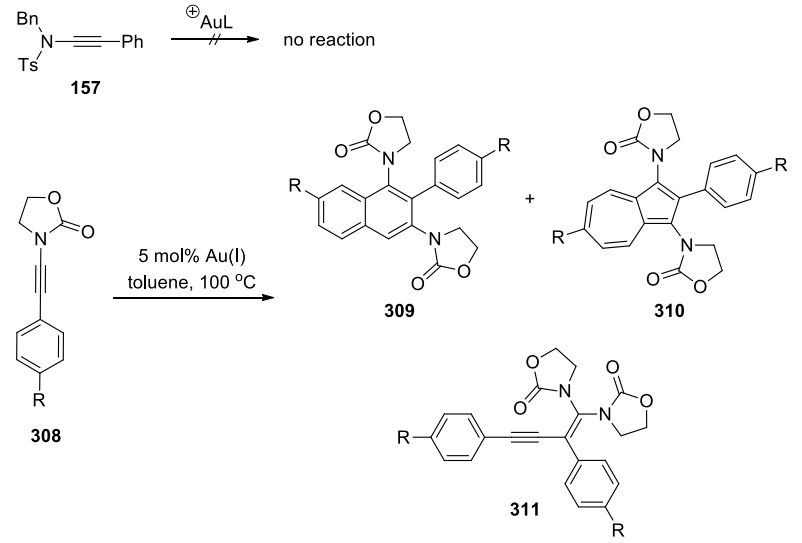
Scheme 125: Cyclization of epoxy-ynamides.

Gold-mediated cyclization

Gold complexes are strong alkynophilic species. Various cyclizations of ynamides could occur under gold catalysis. Ynamides **305** containing a tosyl or a methoxybenzenesulfonyl group were found to favor a dimerization [129], in which one molecule of ynamide acted as a nucleophile to react with the electrophilic gold-ynamide complex, and the intermediate **A** would be transformed into cyclopentadiene derivative **306** *via* sequential [1,5]-hydride shift / metalla-Nazarov reaction / [1,2]-hydride shift (when R^3 = H) (Scheme **126**). Interestingly, when cycloalkyl groups were introduced at the terminus of the alkyne **E** (R^2-R^3 = cycloalkyl), the insertion of the gold carbene occurred into a C-H bond of the adjacent spirocycloalkyl fragment to deliver tricyclic compounds **307** (79-96%). Aryl-substituted sulfonamide **157** was not able to dimerize, presumably because the aryl group reduces the nucleophilicity of the ynamide. When the *N*-sulfonyl group was replaced by less electron-withdrawing oxazolidone group, dimerization occurred and more complicated fused ring products **309**, **310**, and **311** were obtained (Scheme **127**).

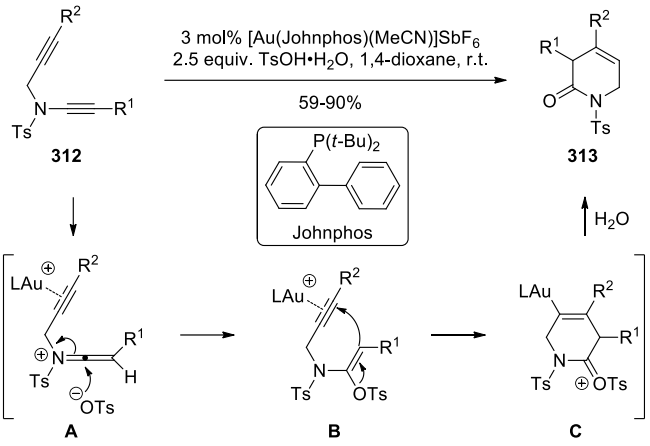


Scheme 126: Dimerization of ynamides.



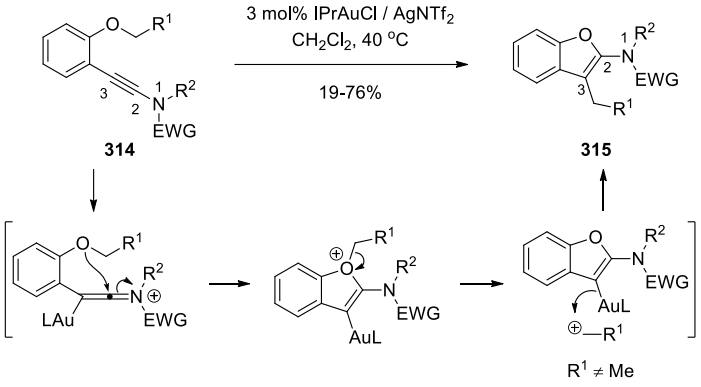
Scheme 127: Dimerization of aryl-substituted ynamides.

In the presence of Au(I) catalyst and TsOH•H_2O as the additive, 5-yne-ynamides **312** could undergo a hydrative cyclization to give 1,6-dihydropyridin-2(3*H*)ones **313** in good yields [130]. A 6-*endo-dig* cyclization of intermediate **B** was proposed to be the key step in the reaction mechanism (Scheme **128**).



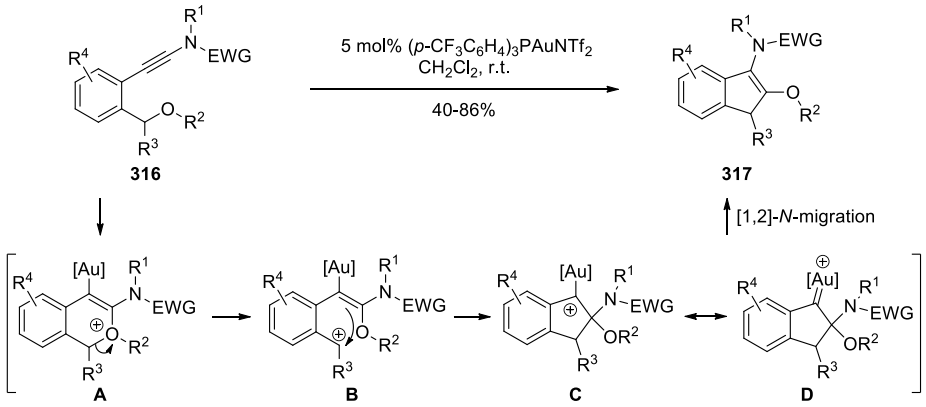
Scheme 128: Synthesis of 1,6-dihydropyridin-2(3*H*)ones.

o-Anisole substituted ynamides **314** were good substrates to synthesize benzofurans. When the *O*-substituents (R^1) were allylic, benzylic, methoxymethyl groups, *etc*. they could migrate from O to C3 position *via* relative stable carbocations following Au(I)-catalyzed 5-*endo-dig* cyclization of ynamides [131] (Scheme **129**).



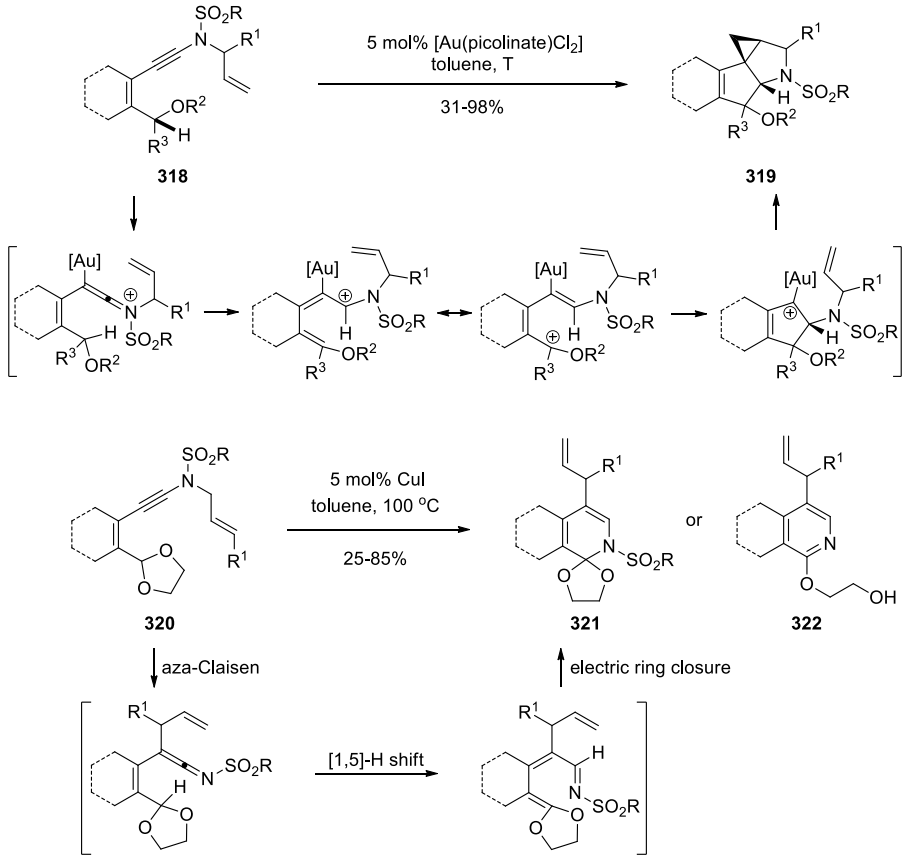
Scheme 129: Synthesis of benzo[*b*]furans.

With $(p\text{-}CF_3C_6H_4)_3PAuNTf_2$ catalyst, ynamides **316** could be converted into functionalized indenes **317** in good yields [132] (Scheme **14030**). In this reaction, 6-*endo-dig* cyclization was initiated by the nucleophilic addition of alkoxy group to the electrophilic α-carbon of the ynamide, giving the intermediate **A.** Followed by that, benzyl C-O cleavage by the vinyl gold intermediate **B** delivered the α-hemiaminal gold carbene **D**, which was terminated by 1,2-*N*-migration to give **317**.



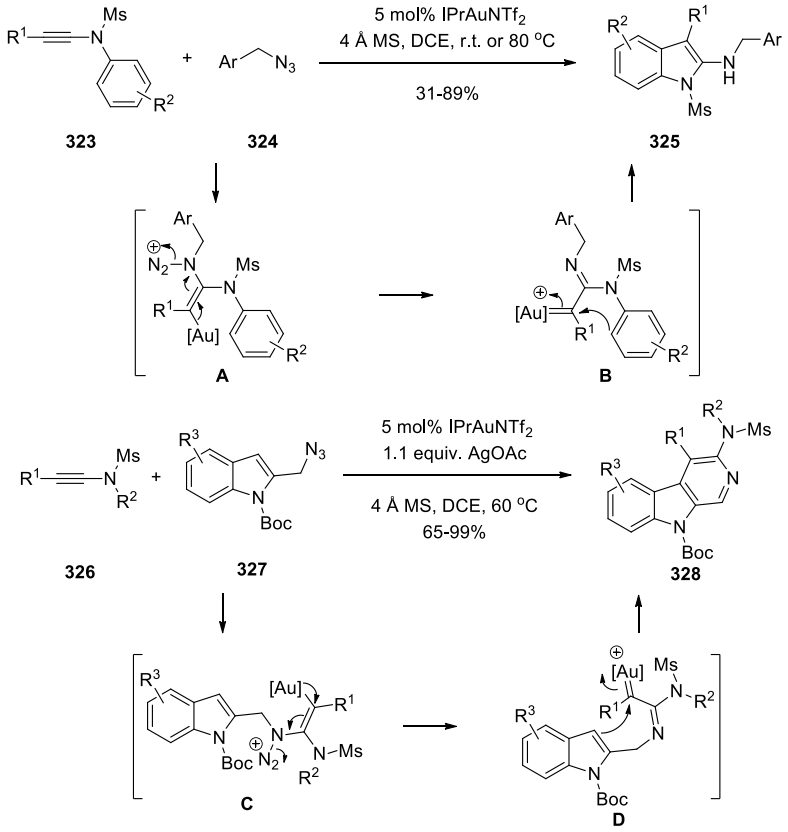
Scheme 130: Synthesis of functionalized indenes.

Regarding the *N*-allyl ynamides **318**, the use of [Au(picolinate)Cl_2] and appropriate reaction temperature (≥ 50 °C) favored the C-H insertion to the ynamide moiety, which initiated subsequent polycyclization to form new polycyclic products **319** [133] (Scheme **131**). This was a different reaction pattern from the previous case. The authors also found that in the presence of CuI, the *N*-allyl ynamides **320** would undergo a cascade aza-Claisen rearrangement, [1,5]-hydride shift, and electric cyclization to generate isoquinoline derivatives **321** or **322**.



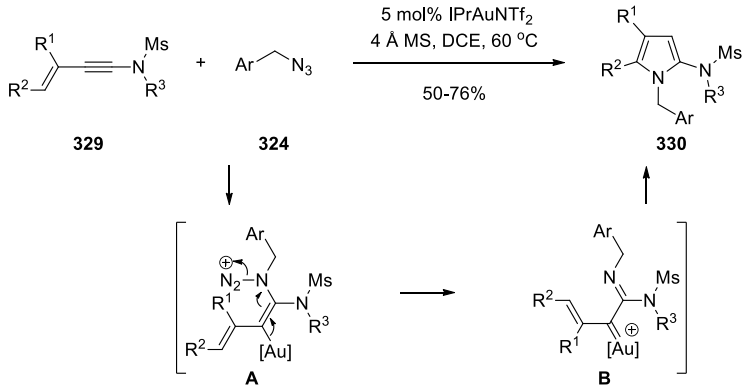
Scheme 131: C-H insertion-cascade cyclization of *N*-allyl ynamides.

In the presence of $IPrAuNTf_2$, benzyl azide **324** would attack the ynamide substrate **323** to form α-imino gold carbene intermediate **B** [134], which could be trapped by the *N*-aryl group from the ynamide moiety and yield to the product 2-aminoindole **325** with 2-amino group from azide and the N atom in the indole ring from ynamides (Scheme **132**). The authors later found that when indolyl azides **327** were used, the α-imino gold carbene intermediate **D** would be trapped by the more nucleophilic indolyl part rather than the *N*-aryl group of the ynamide moiety, which led to 3-amino-β-carbolines **328** as the final products.



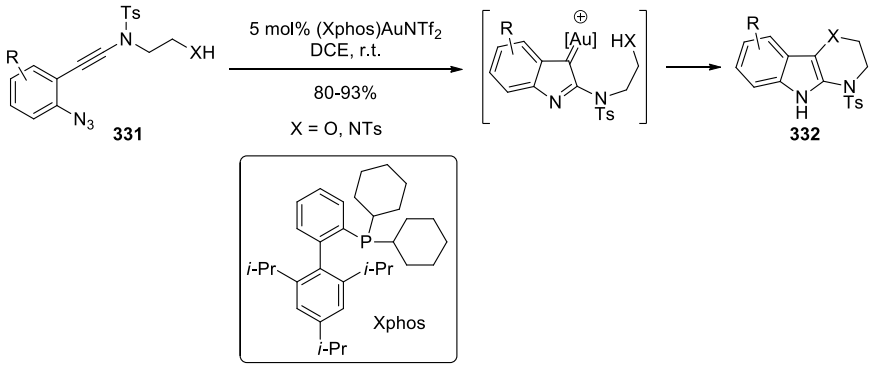
Scheme 132: Gold-catalyzed reaction of azides with ynamides.

When 3-en-1-ynamides **329** were used as the substrates, a formal aza-Nazarov cyclization would take place after the Au(I)-catalyzed alkyne amination of 3-en-1-ynamides and benzyl azides, which led to the highly regioselective synthesis of functionalized 2-aminopyrroles **330** [135] (Scheme **133**).



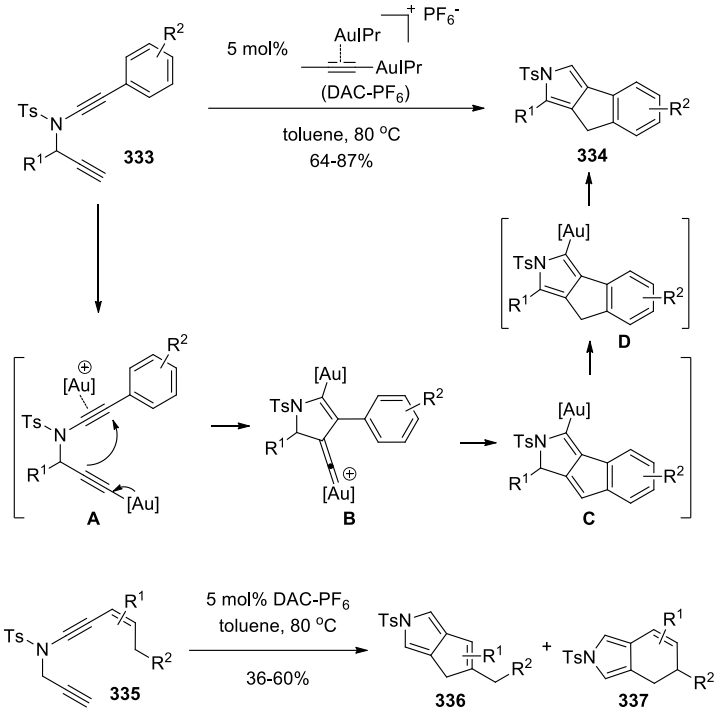
Scheme 133: Synthesis of functionalized 2-aminopyrroles.

The intramolecular version of Au-catalyzed alkyne amination / cyclization was also investigated. Starting from the (azido)ynamides **331**, [1,4]oxazine[3,2-*b*] indoles and 1*H*-pyrazino[2,3-*b*]indoles **332** could be generated in good yields [136] (Scheme **134**).



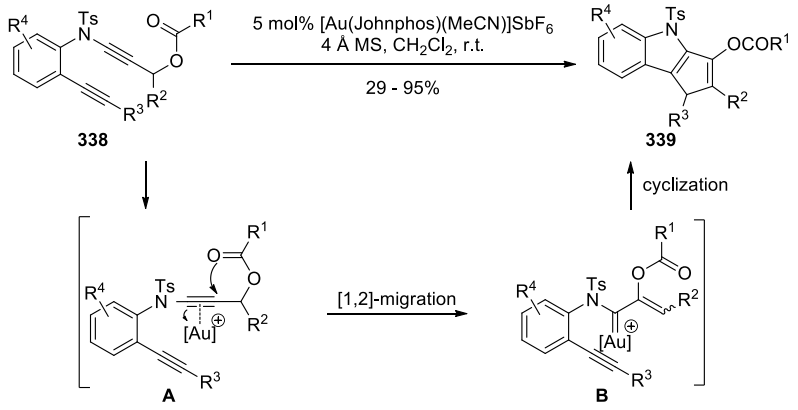
Scheme 134: Gold-catalyzed cascade cyclization of (azido)ynamides.

Hashmi, Ohno, and co-workers [137] developed a novel transformation from *N*-propargyl ynamides **333** to tricyclic pyrroles **334** by the use of a cationic dual-activation gold catalyst (DAC-PF_6). The first cyclization started with the β-addition of a gold acetylide onto the ynamide triple bond. The resulting gold vinylidene **B** provoked the C-H insertion to finish the second cyclization (Scheme **135**). Not only aryl substituted ynamides but also alkyl substituted ynamides could undergo this C-H insertion to form polycyclic pyrroles.



Scheme 135: Synthesis of bicyclic and tricyclic pyrroles.

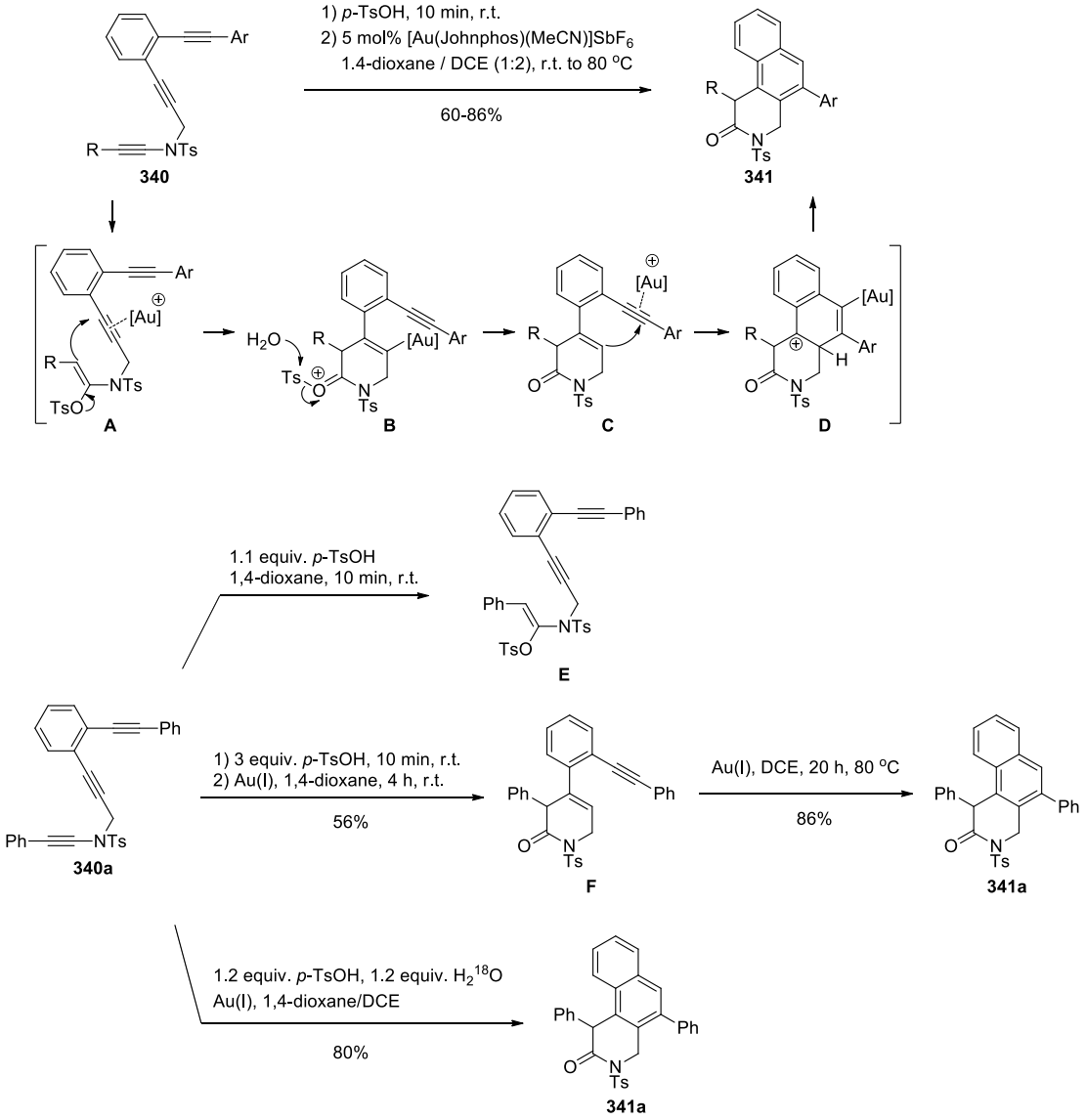
With the catalysis of [Au(Johnphos)(MeCN)]SbF_6, the 1,6-diynes **338** with an ynamide propargyl ester moiety would undergo a 1,2-acyloxy migration and then a cyclization of vinyl gold carbenoid and the pendant triple bond, providing an attractive route to a diverse-substituted cyclopenta[*b*]indoles **339** [138] (Scheme **136**).



Scheme 136: Synthesis of functionalized cyclopenta[*b*]indoles.

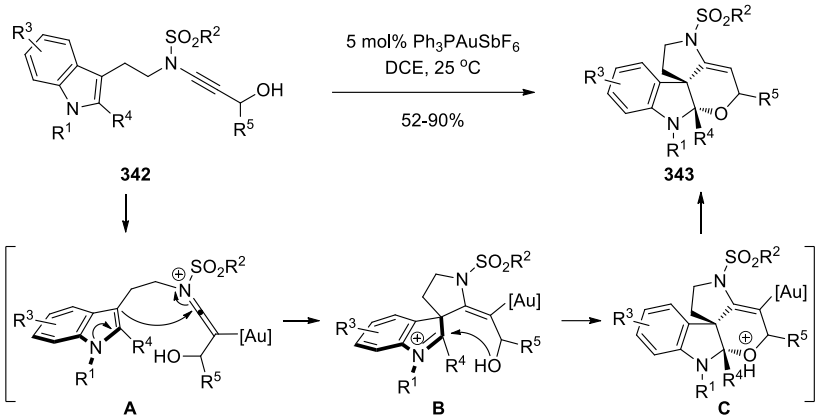
In the presence of [Au(Johnphos)(MeCN)]SbF_6 catalyst, a cascade cyclization from diyne-tethered ynamides **340** to benzo[*f*]dihydroisoquinolones **341** was developed by Sahoo's group [139] (Scheme **137**). Based on the isolation of intermediates and on labeling studies as below, the authors proposed the pathway: the addition of TsO-enamide generated the *N*,*O*-acetal enamide, followed by cleaving the S-O bond to give intermediate **C**. Finally, enyne cyclization and aromatization afforded the

product. The isotopic labeling study of **340a** with *p*-TsOH, $H_2{}^{18}O$ delivered **341a** without incorporation of ^{18}O, which further explained the oxygen source should come from *p*-TsOH rather than the water.



Scheme 137: Synthesis of benzo[*f*]dihydroisoquinolones and the control experiments.

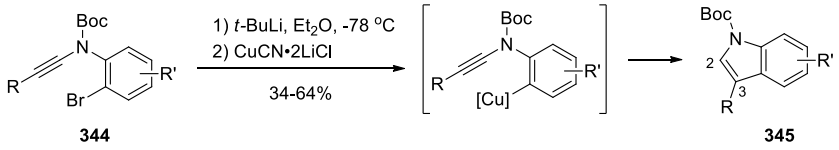
Analogously, by taking advantage of the nucleophilicity of the indole ring, Gong, Yang, and co-workers [140] achieved the synthesis of tetracyclic spirocyclic pyrrolidinoindolines **343** bearing an all-carbon quaternary stereocenter from linear indole-ynamide substrates **342** in a single step catalyzed by Au(I) (Scheme **138**).



Scheme 138: Synthesis of spirocyclic pyrrolidinoindolines.

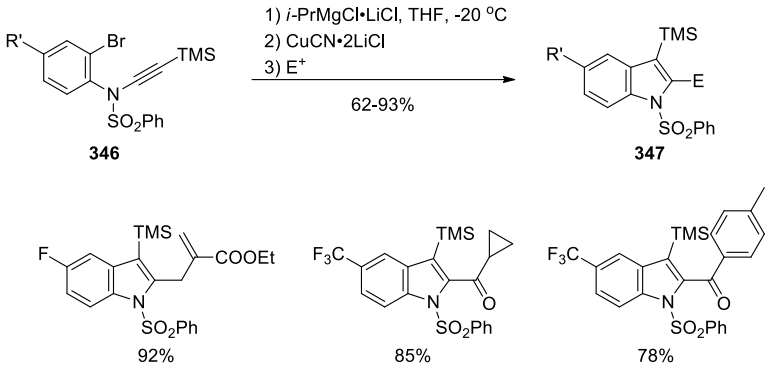
Copper-mediated cyclization

Upon bromine / lithium exchange with *t*-BuLi and subsequent transmetalation with CuCN•2LiCl, *N*-(2-bromophenyl)ynamides **344** underwent an intramolecular 5-*endo*-*dig* carbocupration to give indoles **345** in moderate yields [141] (Scheme **139**). This method was a modular synthesis of 3-substituted indoles, with no substituent at 2-position.

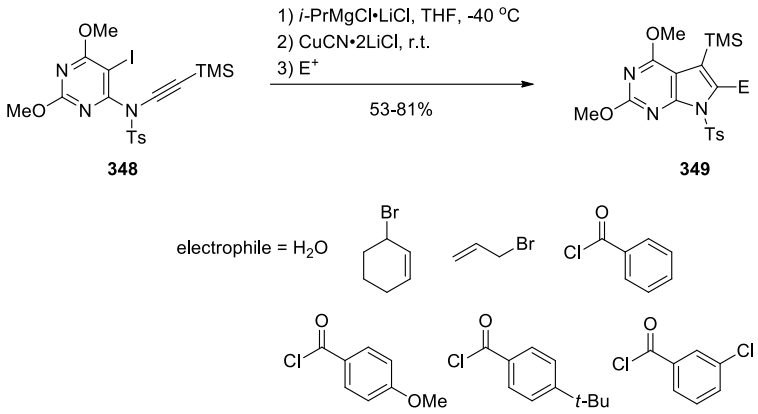


Scheme 139: Intramolecular carbocupration of *N*-aryl-ynamides.

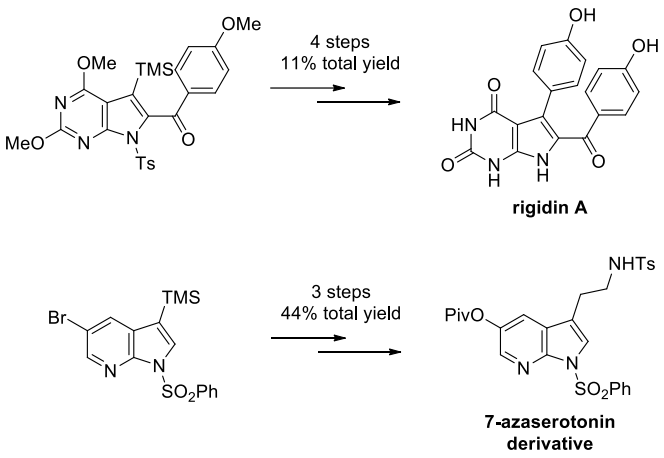
Knochel's group [142] also reported a similar intramolecular carbocupration of ynamides to synthesize indoles and azaindoles. *i*-PrMgCl•2LiCl was used to trigger the bromine / magnesium exchange in the first step. After the 5-*endo*-*dig* carbocupration, various electrophiles (*e.g.* 2-bromomethyl acrylate, cyclopropanecarbonyl chloride, and 4-methylbenzoyl chloride) were used to trap the copper intermediate, which allowed for an easy functionalization at the 2-position of resulting indoles **347** (Scheme **140**). The authors later applied this methodology to the synthesis of pyrrolo[2,3-*d*]pyrimidines **349** (Scheme **141**) and successfully completed the formal synthesis of the marine alkaloid rigidin A and a derivative of 7-azaserotonin [143] (Scheme **142**).



Scheme 140: Synthesis of functionalized indoles.



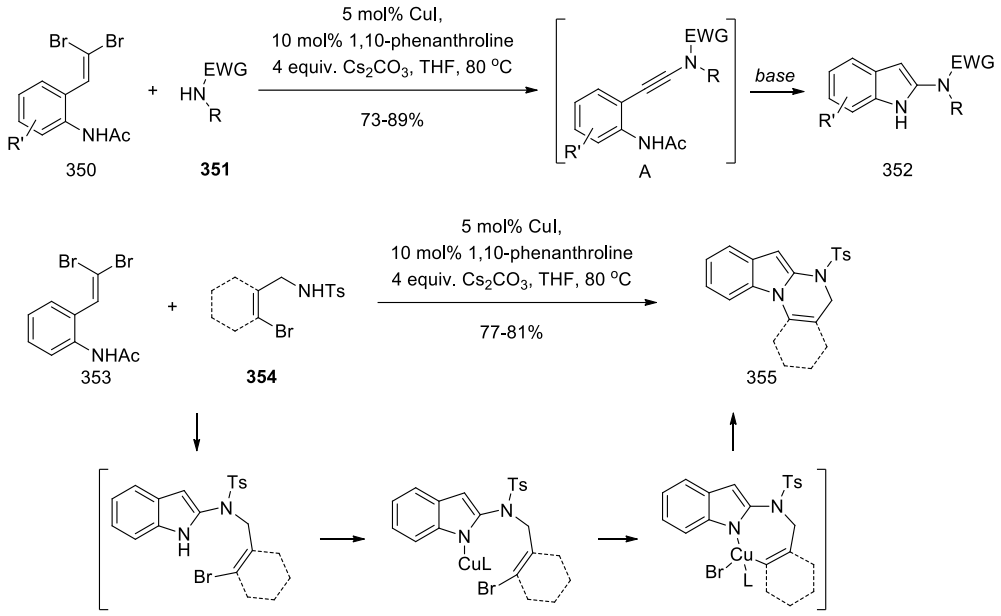
Scheme 141: Synthesis of pyrrolo[2,3-*d*]pyrimidines.



Scheme 142: Synthesis of Rigidin A and a 7-azaserotonin derivative.

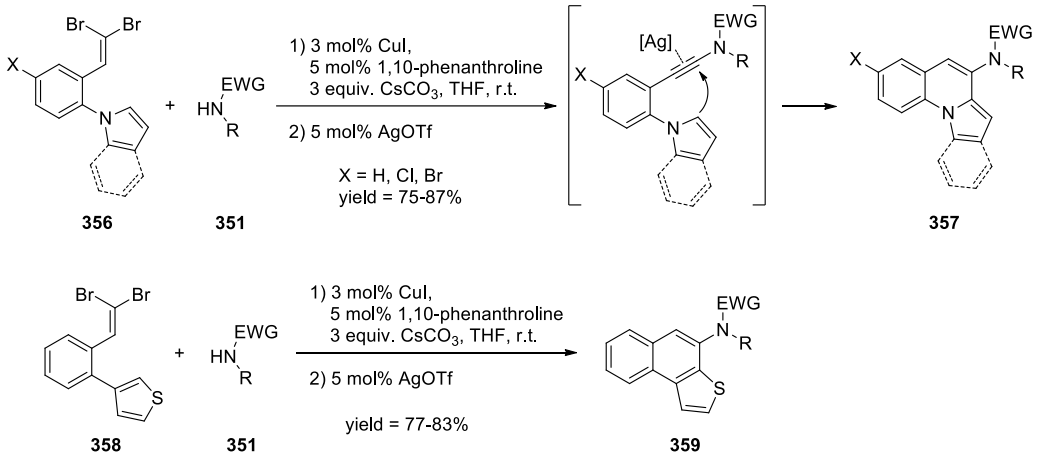
Cu(I)-catalyzed coupling reactions of organo halides and amides is a powerful method to synthesize ynamides. Perumal's group [144] reported that for certain functionalized precursors, the resulting ynamides could further undergo cyclization under the same catalytic conditions. For example, in the presence of CuI, 1,10-phenanthroline, and Cs_2CO_3, *in situ* generated ynamide from the coupling reaction of *gem*-dibromovinylanilide **350** and sulfonamide **351** would undergo a base-promoted

intramolecular hydroamination to afford 2-amidoindoles **352** in good yields (Scheme **143**). When *N*-tosyl-*o*-bromobenzamide **354** was used as the reaction precursor, after the base-promoted intramolecular hydroamination, the N atom on the indole ring would couple with the proximal aryl halide *via* catalyst to afford the *N*-arylation product indolo[1,2-*a*]quinazoline **355**.



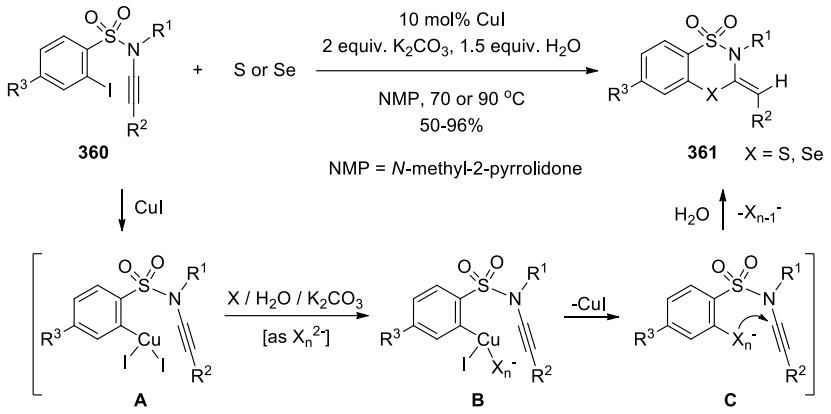
Scheme 143: Synthesis of 2-amidoindoles and indolo[1,2-*a*]quinazolines.

The authors also reported another similar one-pot protocol from *gem*-dibromovinyls **356** (and **358**) and sulfonamides to achieve pyrrolo- / indolo[1,2-*a*]quinolones **357** and naphtha[2,1-*b*]thiophenes **359** [145] (Scheme **144**). The AgOTf-catalyzed intramolecular hydroarylation was crucial in this one-pot reaction to build up fused heterocycles.



Scheme 144: Synthesis of pyrrolo- / indolo[1,2-*a*]quinolines and naphtho[2,1-*b*]thiophenes.

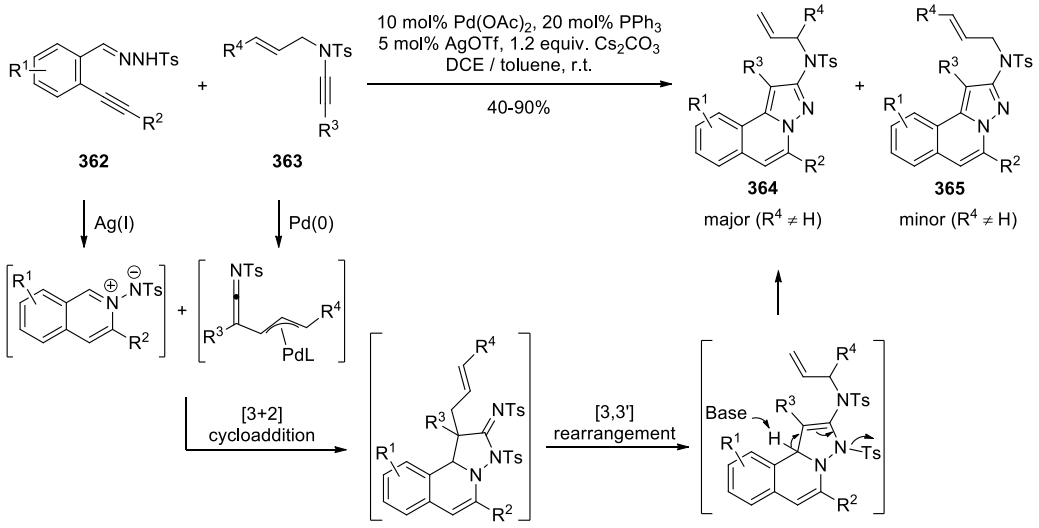
Kumara Swamy's group [146] developed a novel and efficient Cu(I)-catalyzed cyclization of functionalized ynamides, which was achieved through oxidative addition of *N*-alkynyl-2-iodo-benzenesulfonamide **360** to CuI generated intermediate **A**, ligand exchange with S or Se (possibly in the form of S_n^{2-} or Se_n^{2-}, with the presence of water and base) to **B**. Reductive elimination of CuI formed the S or Se functionalized intermediate **C** with subsequent cyclized nucleophilic addition to ynamides and protonation gave the final product benzo[1,4,2]dithiazine-1,1-dioxides or benzo[1,4,2]diaselenazine-1,1-dioxides **361** (Scheme **145**). The resulting enamides has an excellent *Z* configuration.



Scheme 145: Tandem cyclization of functionalized ynamides.

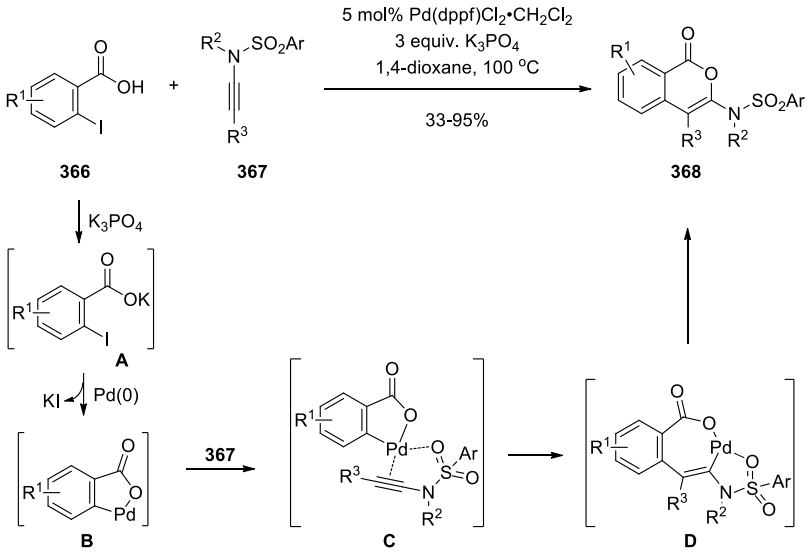
Palladium-mediated cyclization

It was known that Pd catalyst was crucial for the generation of ketenimine intermediate from *N*-allyl ynamide and AgOTf was an effective catalyst for the cyclization of *N*'-(2-alkynylbenzylidene)hydrazide. Based on that, Chen, Peng, and co-workers [147] developed a Pd and Ag co-catalyzed reaction of *N*'-(2-alkynylbenzylidene)hydrazides **362** and *N*-allyl ynamides **363** to synthesize 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines **364** in good yields (Scheme **146**). The transformation proceeded through 6-*endo*-cyclization, [3+2] cycloaddition, [3,3']-rearrangement, and aromatization.



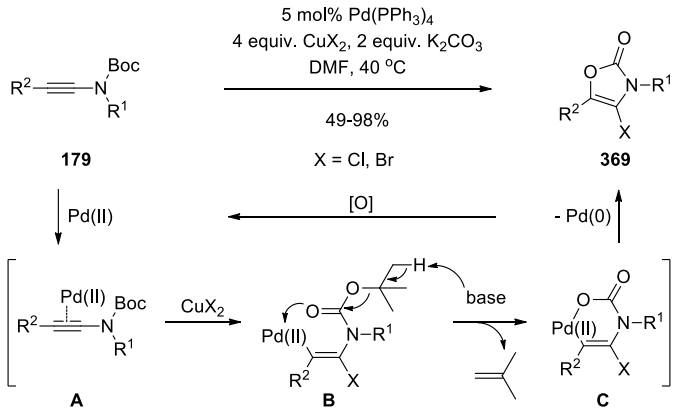
Scheme 146: Synthesis of 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines.

To build up 3,4-disubstituted isocoumarins which were of biological value, a Palladium-catalyzed annulation of 2-iodoaromatic acids **366** with ynamides **367** was developed [148] (Scheme **147**). Under basic conditions, oxidative addition and ligand exchange with 2-iodobenzoate **A** provided cyclopalladated intermediate **B**. Carbopalladation of ynamides regioseletively and reductive elimination furnished the desired isocoumarins **368**.



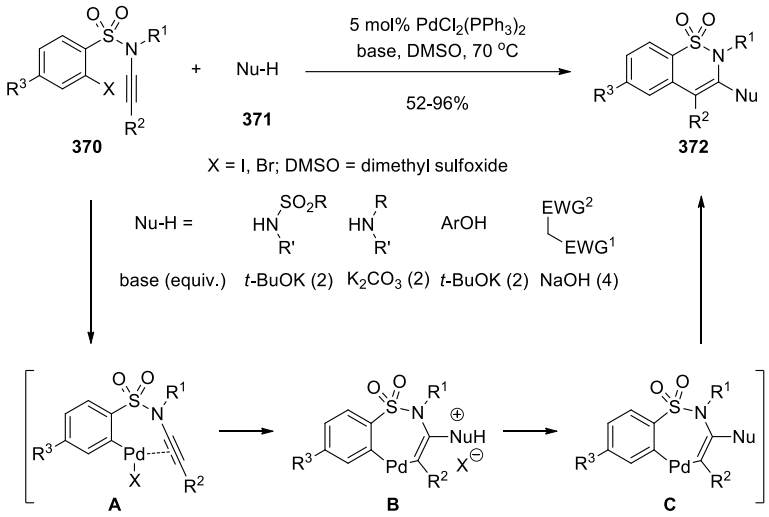
Scheme 147: Synthesis of 3,4-disubstituted isocoumarins.

With $CuCl_2$ or $CuBr_2$ as halide source, *N*-alkynyl alkyloxycarbamates **179** could undergo a $Pd(PPh_3)_4$-catalyzed intramolecular cyclization to form 4-halo-oxazolones **369** [149] (Scheme **148**). It is proposed that halopalladation of the ynamide delivers halo-enamide **B**, which undergoes the ligand exchange with Boc group and releases the product by reductive elimination of C-O bond, with Pd(0) released, being oxidized by copper (II).



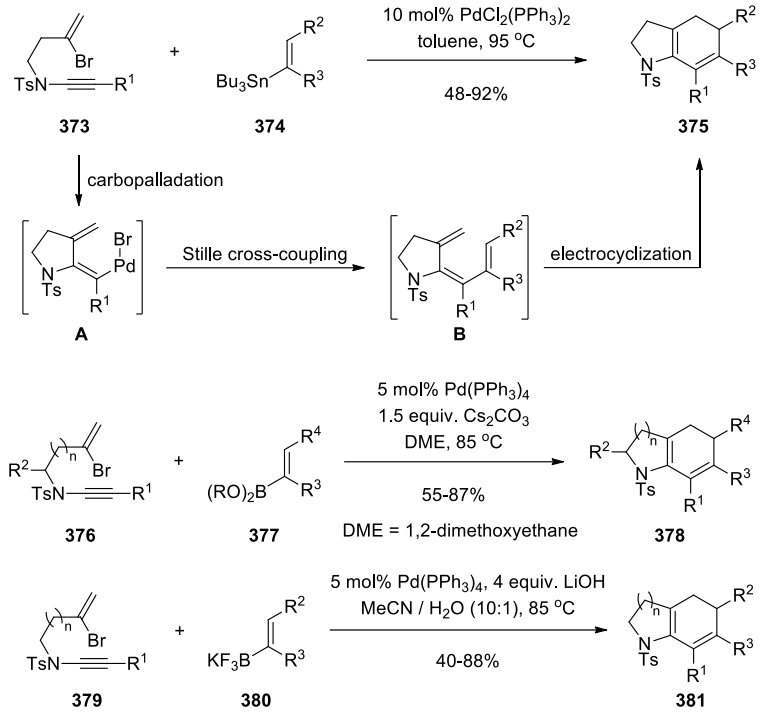
Scheme 148: Synthesis of 4-halo-oxazolones.

The pharmaceutically attractive benzosultams could be synthesized *via* a Palladium-catalyzed tandem cyclization of *N*-alkynyl-2-halobenzenesulfonamides **370** and various nucleophiles **371** [150] (Scheme **149**). The key step in the proposed pathway highlighted the nucleopalladation of ynamides, offering functionalized product **372**.



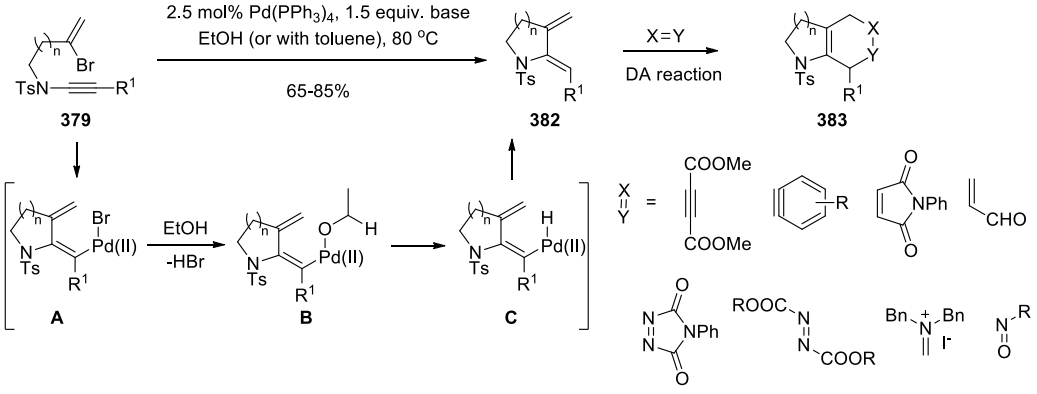
Scheme 149: Synthesis of benzosultams.

Based on the carbopalladation of bromoenynamides (*e.g.* **373**), the Anderson's group [151] developed a series of cascade cyclizations for diverse azacycles. The resulting Pd intermediate **A** from the carbopalladation could undergo a Stille cross-coupling with alkenyl tin reagents **374** and a subsequent 6-electrocyclization to generate bicyclic aminodienes **375** (Scheme **150**). The Suzuki cross-coupling could also be incorporated in this cascade strategy when the coupling partner was alkenylboronic acids and esters **377** [152], or potassium alkenyltrifluoroborate salts **380** [151].



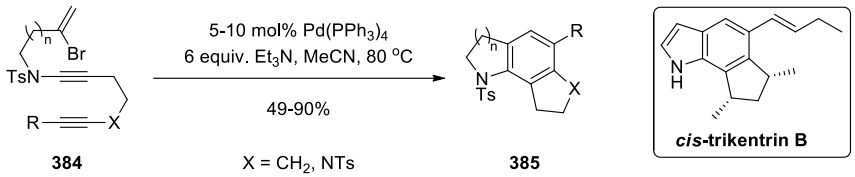
Scheme 150: Synthesis of bicyclic aminodienes.

With alcohols serving as a hydride source in the reaction, the carbopalladation intermediate **A** could be transformed into monocyclic dienamide **382** after β-H-Pd elimination and reductive elimination [153,151] (Scheme **151**). The resulting monocyclic dienamides could be further used in (hetero) Diels-Alder cycloadditions to build up useful polycyclic compounds **383**.



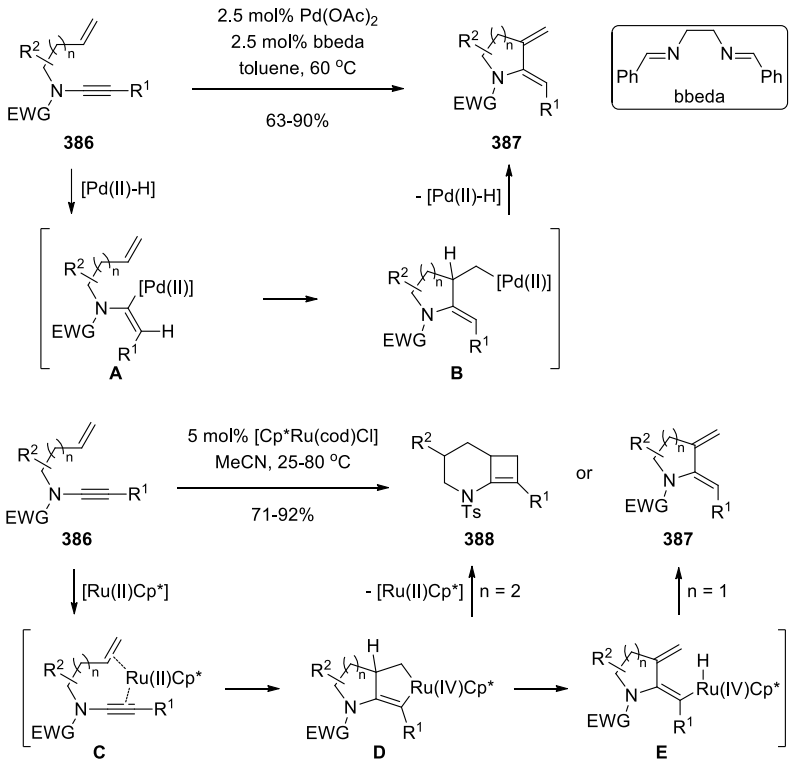
Scheme 151: Synthesis of cyclic dienamides and azacycles.

When the bromoenynamides were installed with another alkyne moiety, the Palladium-catalyzed cascade cyclization afforded azatricyclic products **385** with trikentrin-like framework [154] (Scheme **152**).

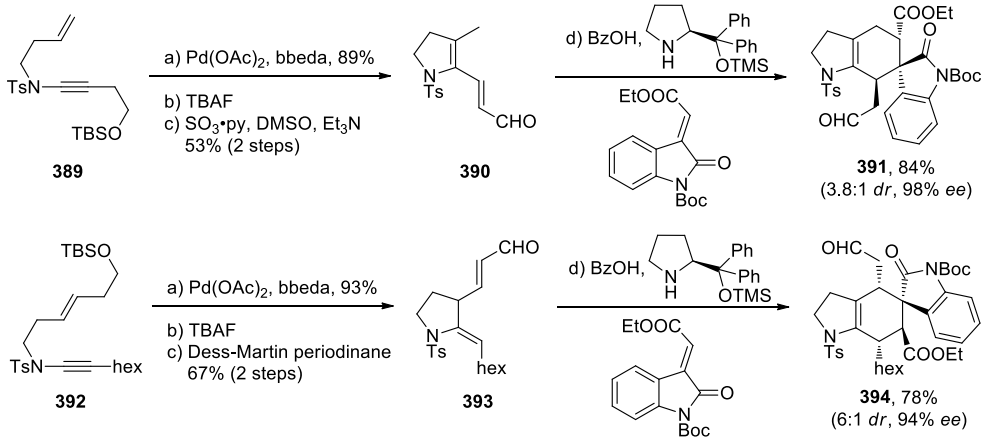


Scheme 152: Synthesis of azatricycles.

The cycloisomerization of 1,6- and 1,7-enynamides **386** proceeds in the presence of Pd or Ru catalyst. This was another efficient approach to access cyclic dienamides **387** [155] (Scheme **153**). In the Pd catalytic cycle, regioselective hydropalladation of ynamide affords the alkenylpalladium intermediate **A**. Carbopalladation of the alkene gives the enamidyl cyclized alkylpalladium species **B**, which undergoes β-hydride elimination to deliver the diene product **387**. Compared with palladium catalysis, Ruthenacycle **D** is formed *via* oxidative cyclometallation. When n = 2, reductive elimination leads to the 6,4-fused cyclobutene product **388**. When n = 1, the ring strain of 5,5-fused ruthenacycle would prohibit the direct reductive elimination, which then favors the β-hydride elimination and a subsequent reductive elimination to yield the diene product **387**. Pyrrolidinyl dienals (**390** and **393**) could also be prepared by this Pd-catalyzed cycloisomerization, followed by desilylation and oxidation. The chiral pyrrolidine catalyst (Jørgensen-Hayashi catalyst) could transform dienal substrates into chiral conjugated trienamine intermediates, which further trigger the Diels-Alder reactions with oxindole to generate polysubstituted hexahydroindoles (**391** and **394**) in excellent enantioselectivities [156] (Scheme **154**).



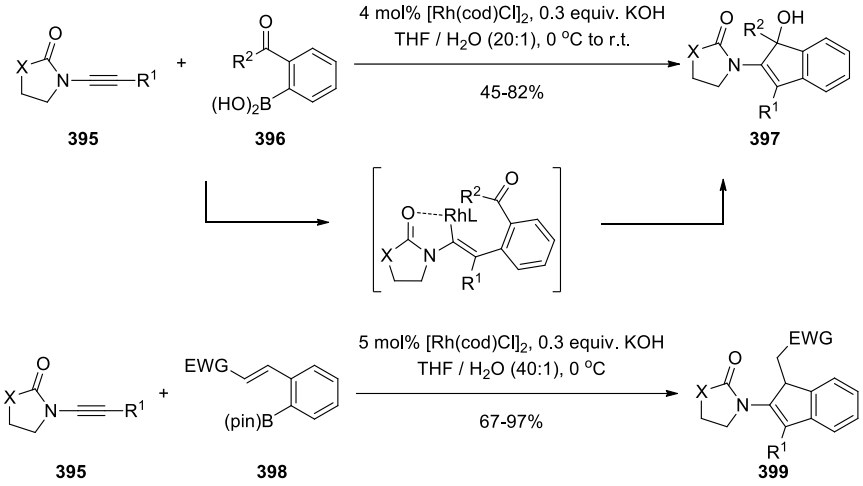
Scheme 153: Synthesis of cyclic dienamides from 1,n-enynamides.



Scheme 154: Synthesis of polysubstituted hexahydroindoles.

Rhodium-mediated cyclization

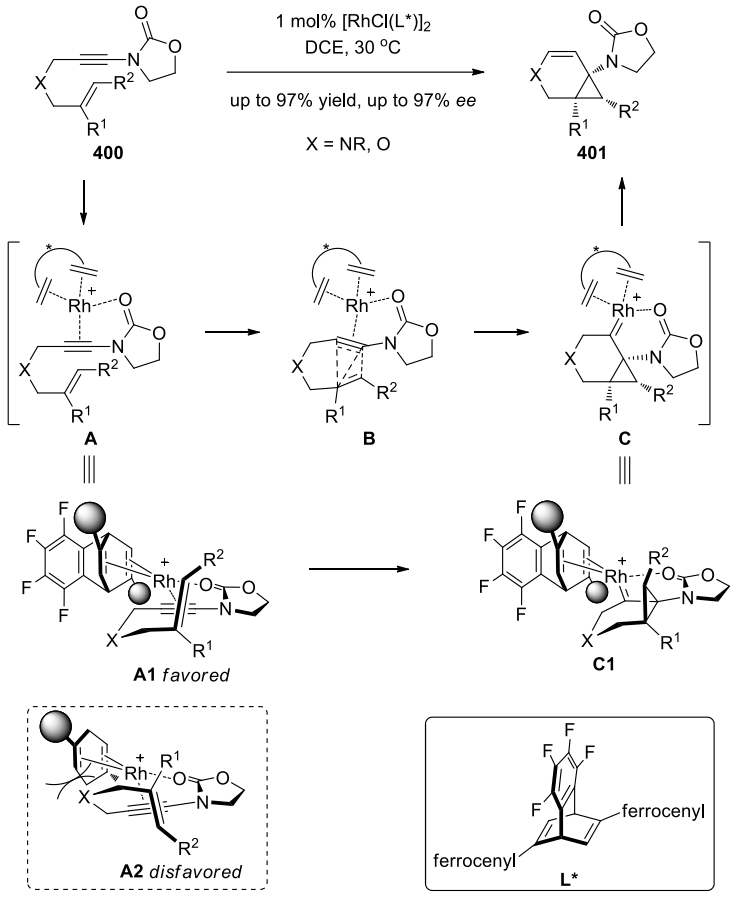
Lam's group once developed a rhodium-catalyzed hydroarylation of ynamides with arylboronic reagents [71]. The regioselective carbo-rhodation of ynamides is assisted by the 5-membered chelation of the oxazolidinone with the rhodium. Terminated by alkenyl rhodium insertion of the ketones / aldehydes, 2-amidoindenols **397** or 2-amidoindenes **399** were released [157] (Scheme **155**).



Scheme 155: Annulation of ynamides with bifunctional arylboron reagents.

Hishimura, Hayashi, and co-workers [158] disclosed a rhodium-catalyzed asymmetric cycloisomerization of heteroatom-bridged 1,6-enynamides **400** to yield functionalized 3-aza- and oxabicyclo[4.1.0]heptene derivatives **401** (Scheme **156**). The reaction was proposed to undergo a 6-*endo* cyclization *via* the electrophilic activation of an alkyne moiety by π-acidic Rh catalyst to form a Rh-carbenoid species **C**, and a subsequent 1,2-hydrogen shift to furnish the bicyclic backbone. Conformation **A1** is favored where the X group (NR or O) is placed at a less bulky site, whilst the conformation

A2 suffers from a repulsion between the X group and the ferrocenyl group of the ligand L*. Therefore, the cyclization of **A1** gives the Rh-carbenoid **C1**, which finally delivers the chiral product **401** in high enantioselectivity.

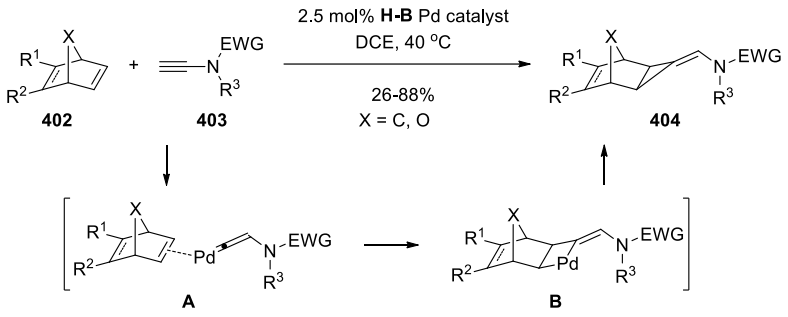


Scheme 156: Synthesis of functionalized 3-aza- and oxabicyclo[4.1.0]heptene derivatives.

Cycloaddition

[2+1]

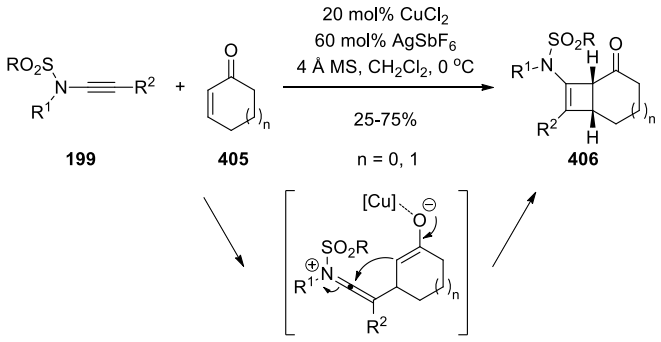
Terminal ynamides **403** could work with one-carbon synthon to achieve a formal [2+1] cycloaddition with strained C-C double bonds (like those in norbornene or its derivatives **402**) in the presence of **H-B** Pd catalyst (Hermann-Beller phosphapalladacycle) [159]. According to the authors' previous study on the palladium-catalyzed [2+1] cycloaddition of terminal alkynes to norbornene derivatives [160, 161], this reaction might experience a similar [2+2] cycloaddition of Pd vinylidene species with the double bond of norbornene derivatives, and a reductive elimination to afford the cyclopropane rings **404** (Scheme **157**).



Scheme 157: [2+1] cycloaddition of ynamides with norbornene derivatives.

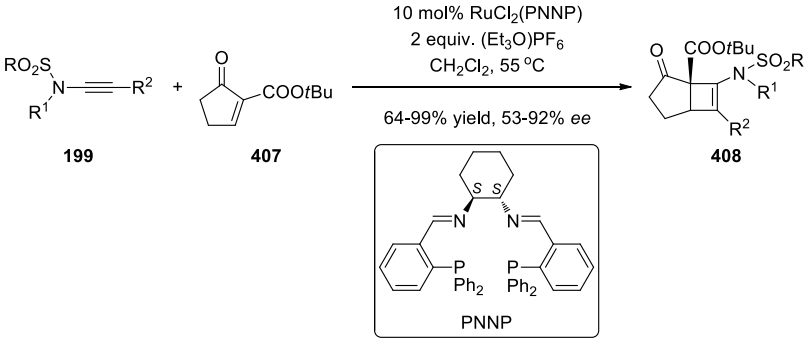
[2+2]

Hsung's group [162] did a pioneering work on demonstrating ynamide could act as an effective reaction partner in Ficini [2+2] cycloaddition. With $CuCl_2$ and $AgSbF_6$ as catalysts, ynamides **199** reacted with enones **405** smoothly to generate the desired cyclobutene products **406** (Scheme **158**).



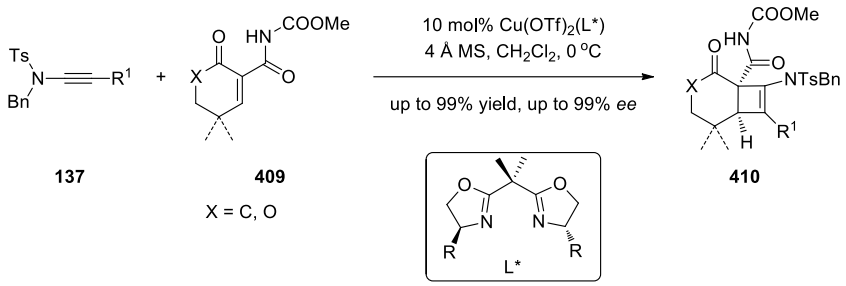
Scheme 158: Copper-catalyzed [2+2] cycloaddition.

Mezzetti's group [163] subsequently developed a ruthenium-catalyzed Ficini cycloaddition of ynamides **199** with unsaturated β-keto esters **407** in good *ees* by applying chiral PNNP (Scheme **159**).



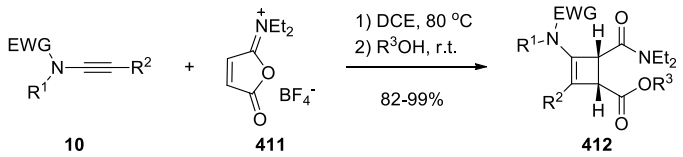
Scheme 159: Ruthenium-catalyzed asymmetric [2+2] cycloaddition.

Another asymmetric Ficini cycloaddition of ynamides **137** with cyclic α-alkylidene β-oxo imides **409** was achieved in the presence of chiral Cu complex [164] (Scheme **160**).



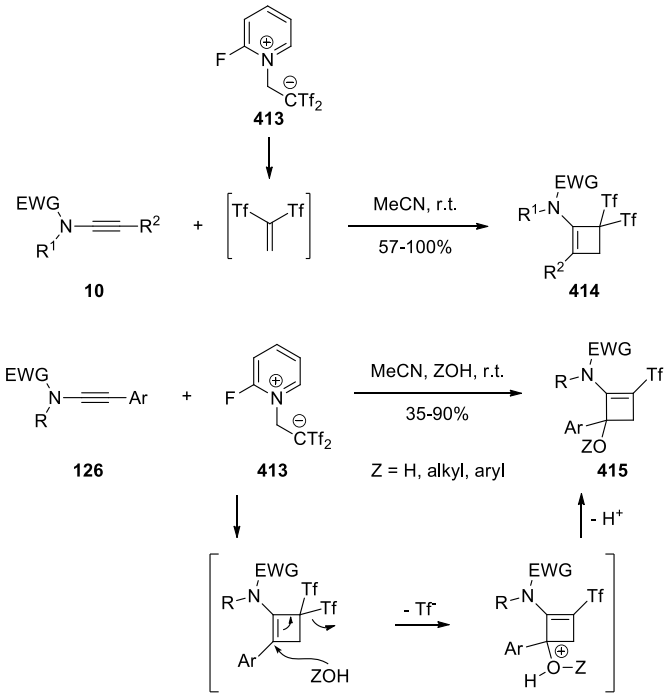
Scheme 160: Copper-catalyzed asymmetric [2+2] cycloaddition.

The first metal-free Ficini cycloaddition was developed by Liu's group [165]. Ynamides **10** reacted with cyclic α,β-unsaturated isoimidium salts **411** to give stable cyclobutenamides **412** in good to excellent yields (Scheme **161**).



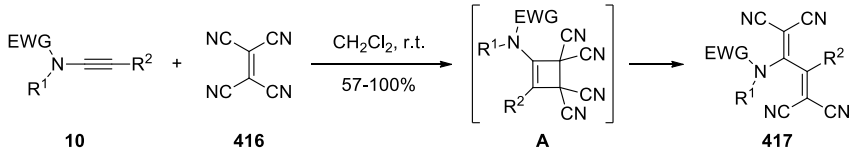
Scheme 161: First case of metal-free Ficini cycloaddition.

Bis(trifluoromethylsulfonyl)ethene ($Tf_2C=CH_2$), which was *in situ* generated from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **413**, was an alternative to the α,β-unsaturated carbonyl compound to participate in Ficini cycloaddition with ynamides **10** under metal-free conditions [166] (Scheme **162**). As for the aryl ynamides **126**, the resulting cyclobutene ring could be attacked by water or alcohols at β-position of enamides, delivering cyclobutenol derivatives **415** by deprotonation.



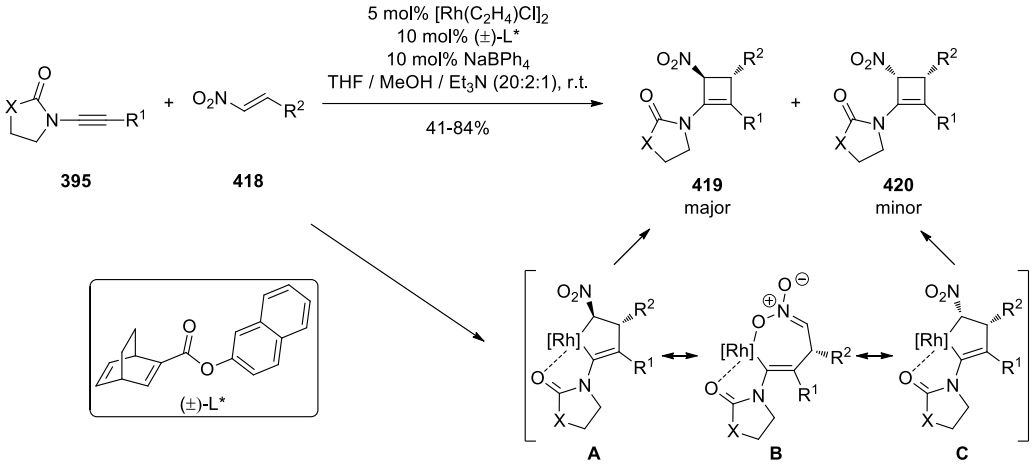
Scheme 162: Metal-free synthesis of aminocyclobutenes and aminocyclobutenols.

A [2+2] cycloaddition of ynamides **10** and tetracyanoethylene (TCNE) **416** could occur at room temperature, however the labile cycloadducts **A** would undergo retroelectrocyclization to provide tetracyanobutadienes **417** [167] (Scheme **163**).



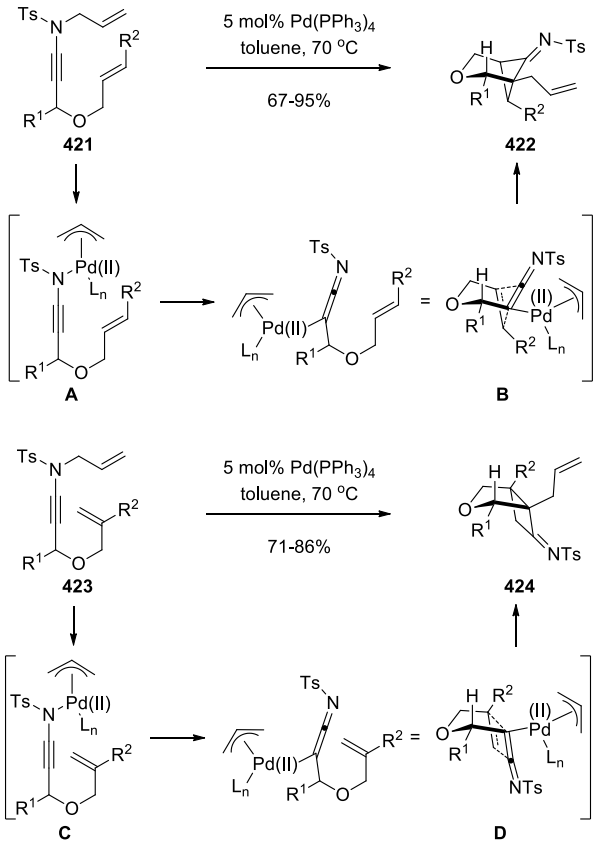
Scheme 163: Synthesis of tetracyanoethylene.

Lam and co-workers [168] reported [2+2] cycloadditions of ynamides **395** and nitroalkenes **418** to deliver cyclobutenamides **419** and **420** in the presence of Rh-diene and $NaBPh_4$. The X-ray crystallographic analysis confirmed that product **419** is the major isomer, with the nitro in *trans*-configuration with the R^2 groups on the cyclobutene ring. By contrast with Ficini cycloaddition's pathway, this reaction was proposed to undergo an oxidative cyclization to form rhodacycle **A** or **C** and subsequent reductive elimination to release the products (Scheme **164**). The five-membered rhodacycle **C** could be switchable to **A** with less sterical repulsion between NO_2 and R_2, *via* a seven-membered rhodacycle **B**.



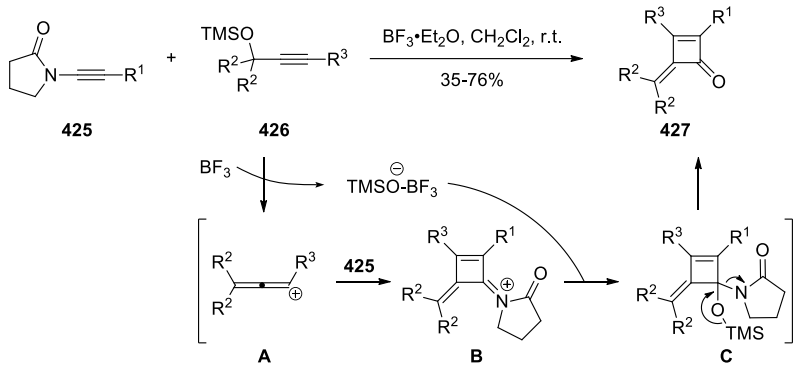
Scheme 164: Rhodium-catalyzed [2+2] cycloaddition.

Hsung's group [169] found that *in situ* generated ketenimine from the palladium-catalyzed N-to-C allyl rearrangement could react with an oxygen tethered alkenyl moiety to realize an intramolecular [2+2] cycloaddition (Scheme **165**). The substrate **421** is supposed to undergo N-to-C allyl rearrangement to generate keteniminyl intermediate **B** with a favorable chair-like conformation, as shown in the scheme. Followed by that, a subsequently [2+2] cycloaddition results in the bridged bicycloimine **422**. As for *gem*-disubstituted alkenyl **423**, the keteniminyl intermediate favors boat-like conformation **D**, leading to fused bicycloimines **424**.



Scheme 165: Palladium-catalyzed intramolecular [2+2] cycloaddition.

In the presence of Lewis acid BF_3•Et_2O, a formal [2+2] cycloaddition between ynamides **425** and propargyl silyl ethers **426** would occur to form alkylidenecyclobutenones **427** [170] (Scheme **166**). The cycloaddition of allenyl cation **A** with ynamides formed iminium intermediate **B** through either a stepwise or a concerted process. TMSO anion later added back to the intermediate **B** and eliminated the oxazolinone moiety, yielding cyclobutenones.

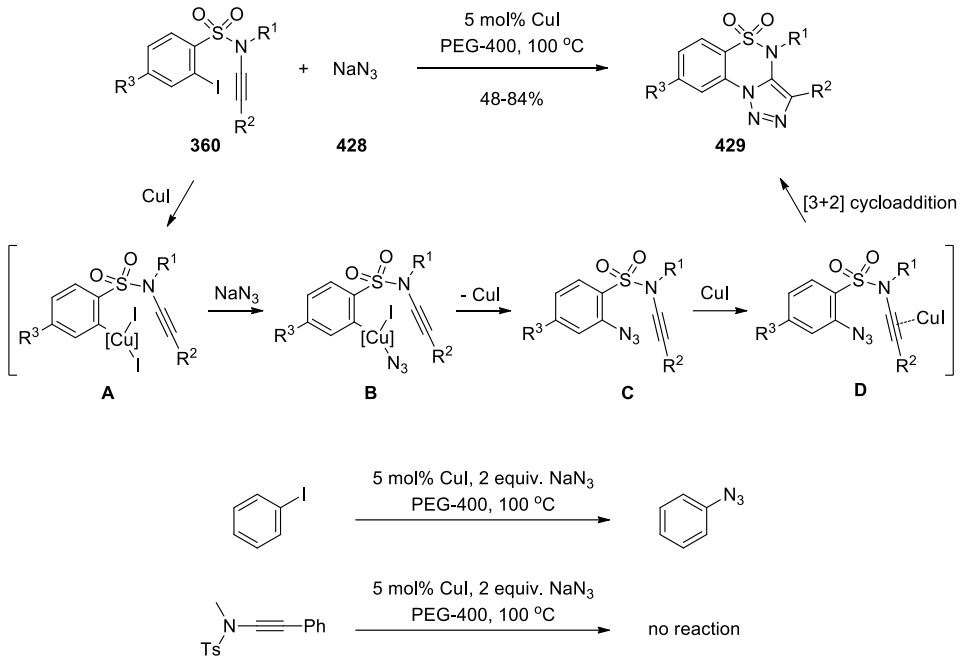


Scheme 166: Lewis acid-catalyzed formal [2+2] cycloaddition.

[3+2]

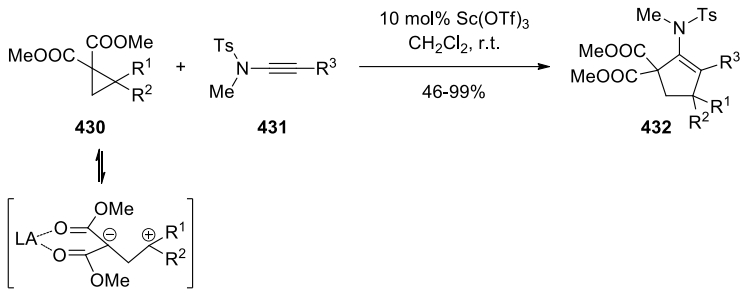
In general, ynamides serve as a two-carbon reaction partner to react with various three-atom (4π electron) synthons (*e.g.* 1,3-dipoles and their equivalents) in [3+2] cycloadditions.

Kumara Swamy's group [171] achieved an intramolecular cycloaddition to synthesize triazolo-1,2,4-benzothiadiazine-1,1-dioxides **429** (Scheme **167**). One main attractive feature of this reaction was using low loading air-stable catalyst (5 mol% CuI) and eco-friendly solvent PEG-400 (polyethylene glycol 400). The control experiment of phenyl iodide with NaN_3 in the presence of CuI demonstrates that the azidobenzene was formed, however the Huisgen cycloaddition of ynamide with NaN_3 did not occur in the absence of phenyl iodide. This implies that the aryl iodide **360** would be essential to generate the azido substituted **C** *via* oxidative addition to CuI, azide exchange, and reductive elimination of CuI. Intramolecular Huisgen cycloaddition of ynamides with the azides affords the fused triazoles **429**.



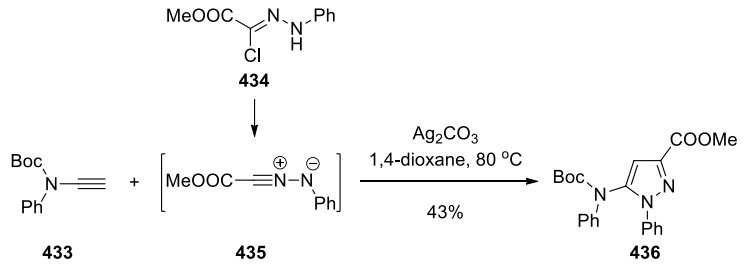
Scheme 167: Synthesis of triazolo-1,2,4-benzothiadiazine-1,1-dioxides.

Another case of 1,3-dipolar synthons is cyclopropanes. With oxophilic Lewis acid $Sc(OTf)_3$, cyclopropanes **430** reacted with ynamides **431** to provide cyclopentene sulfonamides **432** in good to excellent yields [172] (Scheme **168**).



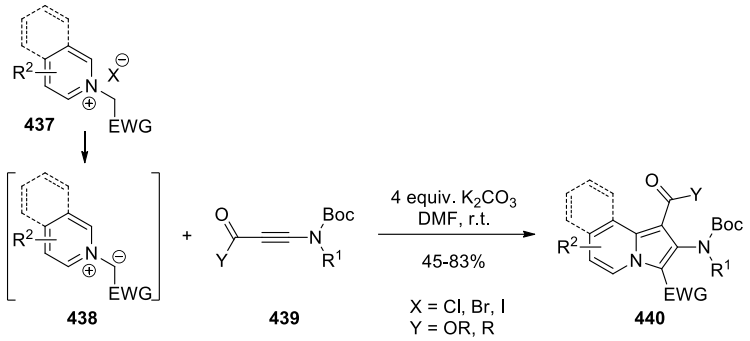
Scheme 168: Synthesis of cyclopentene sulfonamides.

Franchini and co-workers [173] reported the first example of a 1,3-dipolar cycloaddition between *tert*-butyl-*N*-ethynyl-*N*-phenylcarbamate **433** and *C*-carboxymethyl-*N*-phenylnitrilimine **435**, which was generated *in situ* from hydrazonoyl chloride **434**, with Ag_2CO_3 as base (Scheme **169**). Product **436** was the only regio-isomer that was obtained due to an electronic match between two partners.



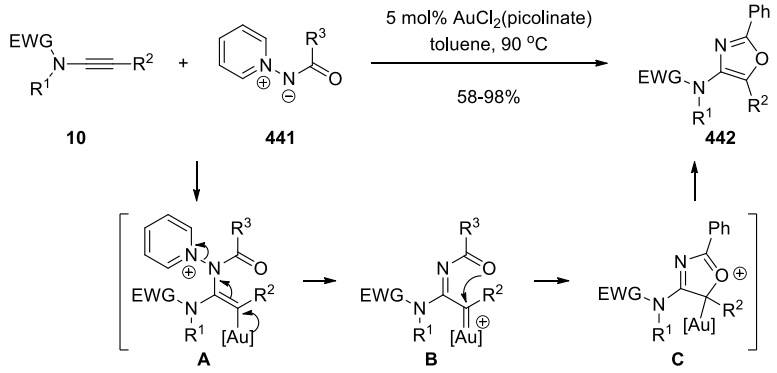
Scheme 169: 1,3-Dipolar cycloaddition of ynamide with nitrilimine.

Electron-deficient ynamides **439**, possessing an ynoate or ynone moiety, could undergo a 1,3-dipolar cycloaddition with stabilized pyridinium ylides **438**, which was generated *in situ* from pyridinium salts **437** with base [174]. Sequential aromatization provided a convenient access to highly functionalized 2-aminoindolizines **440** (Scheme **170**).

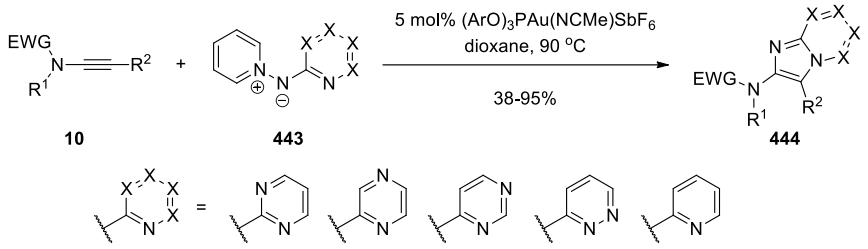


Scheme 170: 1,3-Dipolar cycloaddition of ynamides with pyridinium ylides.

Gold catalyst has been demonstrated as a powerful catalyst to activate ynamide's C-C triple bond and the resulting gold carbenoid is a versatile intermediate to realize diverse transformations. Davies' group [175 , 176] used *N*-acylpyridinium-*N*-aminides **441** as the 1,3-*N*,*O*-dipole equivalent to react with ynamides **10** with $AuCl_2$(picolinate). After the nucleophilic attack of aminide to the gold activated ynamide, the gold carbenoid **B** would be captured by the acyl oxygen intramolecularly with release of a pyridine, which finally led to the cycloadduct 4-aminooxazole **442** (Scheme **171**). Similarly, the 1,3-*N*,*N*-dipole equivalents, pyridinium *N*-(heteroaryl)aminides **443**, were also able to react with ynamides **10** to form imidazo-fused heteroaromatics **444** [177] (Scheme **172**).

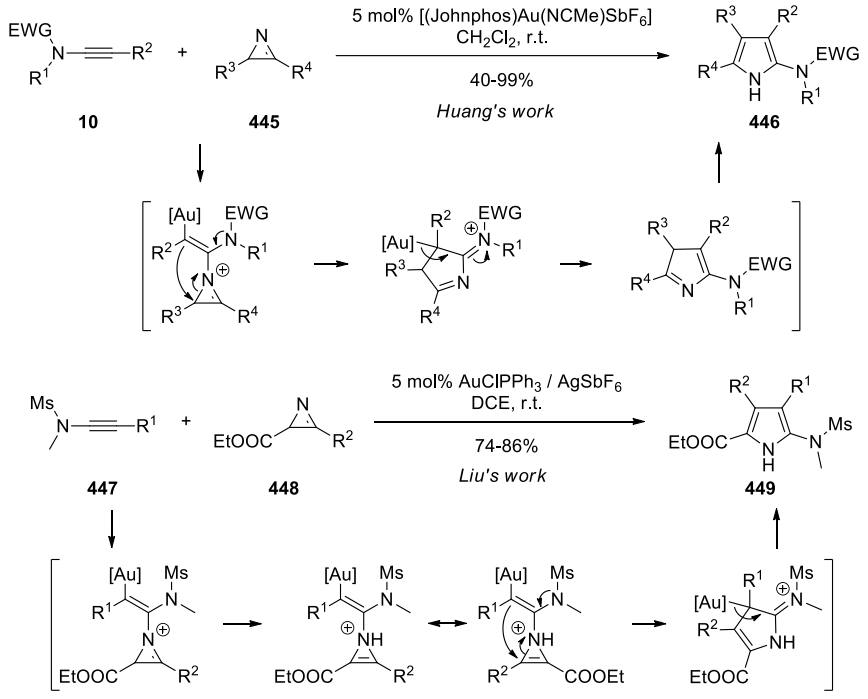


Scheme 171: Synthesis of 4-aminooxazoles.

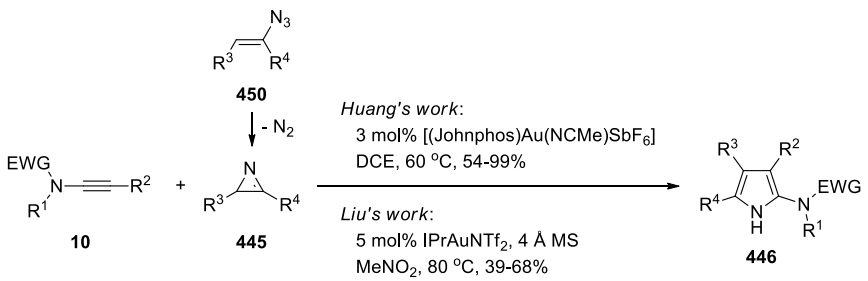


Scheme 172: Synthesis of imidazo-fused heteroaromatics.

Both Huang's group [178] and Liu's group [179] disclosed an atom-economical synthesis of polysubstituted 2-aminopyrroles **446** (and **449**) from 2*H*-azirines **445** (and **448**) and ynamides **10** (and **447**) through a gold-catalyzed nitrene transfer process (Scheme **173**). Alkenyl azides **450**, a "masked" 2*H*-azirines by losing N_2 at elevated temperature, could be used directly in the gold-catalyzed cycloaddition as well [179, 180] (Scheme **174**).

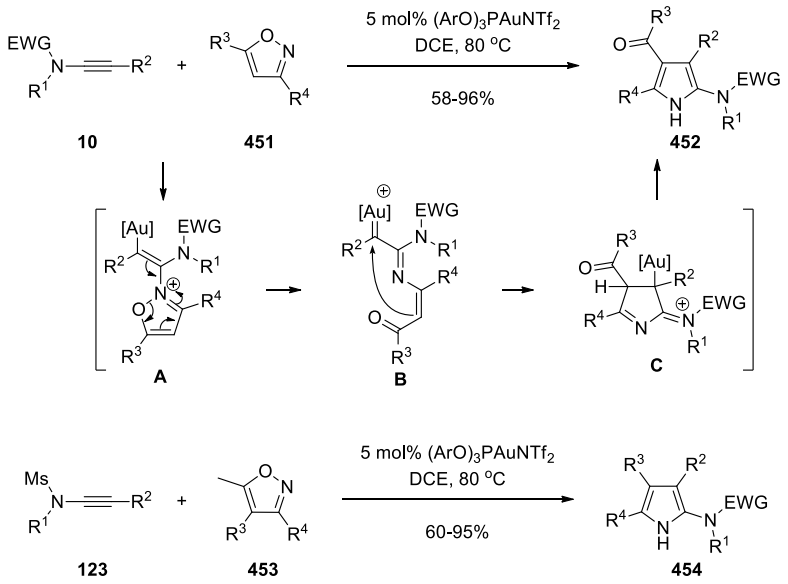


Scheme 173: Formal cycloaddition of ynamides with 2*H*-azirines.

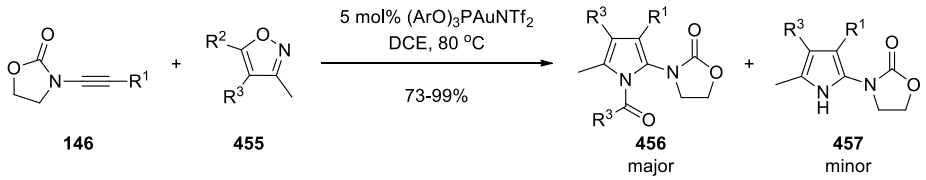


Scheme 174: Formal cycloaddition of ynamides with alkenyl azides.

Ye, Lu, and co-workers [181] found that isoxazoles **451** could also be used in the gold-catalyzed formal [3+2] cycloaddition to form 2-aminopyrroles **452**. After the nucleophilic attack of isoxazole to the gold-activated ynamide, the isoxazole ring would be opened to form a linear gold carbenoid **B**. Subsequent cyclization of the carbenoid led to the formation of the new pyrrole ring system. When fully-substituted isoxazoles **453** were used, de-acylated 2-aminopyrroles **454** was formed instead (Scheme **175**). Furthermore, when *N*-alkynyl oxazolidinones **146** were used as the ynamide substrates, the reaction with fully-substituted isoxazoles **455** would give *N*-acylpyrroles **456** as the major products and de-acylated pyrroles **457** as the minor products [182] (Scheme **176**).

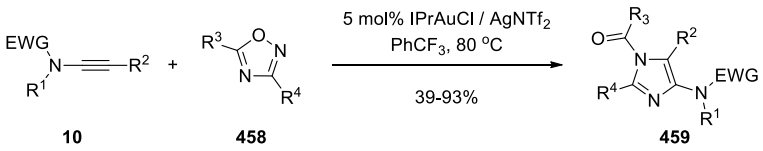


Scheme 175: Cycloaddition of ynamides with isoxazoles.



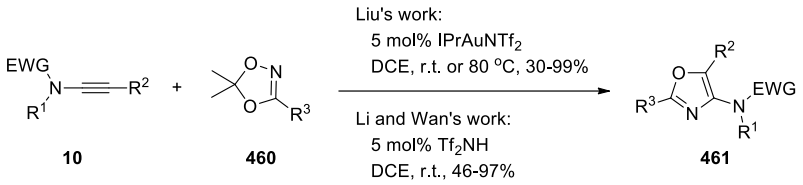
Scheme 176: Cycloaddition of *N*-alkynyl oxazolidinones with fully-substituted isoxazoles.

Such reaction pattern could be extended to the reaction of 1,2,4-oxadiazoles **458** with ynamides **10** by Hashmi's work [183]. It was regarded as an atom-economic access to fully substituted 4-aminoimidazoles **459** (Scheme **177**).



Scheme 177: Synthesis of fully substituted 4-aminoimidazoles.

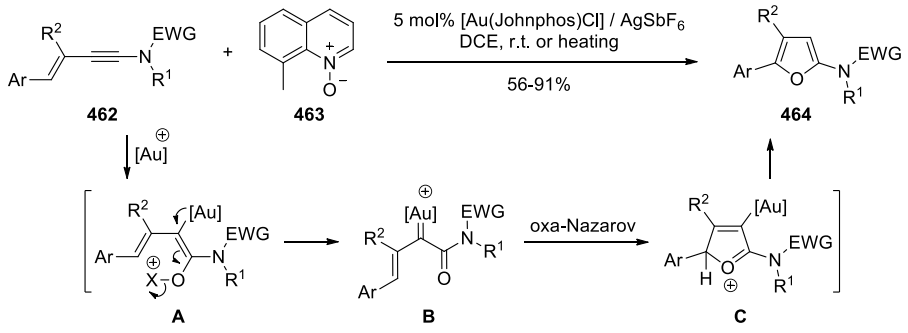
Liu's work [184] demonstrated dioxazole **460** was another five-membered ring precursor that could undergo a gold-catalyzed cycloaddition with ynamides **10** for the synthesis of functionalized oxazoles **461** (Scheme **178**) with one molecular acetone released. Li, Wan, and co-workers [185] further developed a metal-free version. By using 5 mol% Tf_2NH, the reaction afforded the desired 4-aminooxazoles in good yields.



Scheme 178: Cycloaddition of ynamides with dioxazoles.

[4+1]

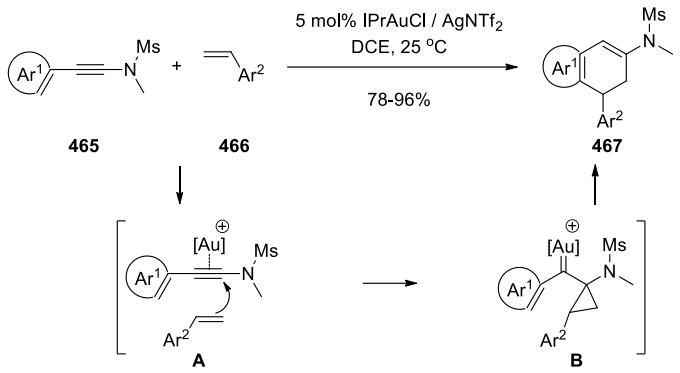
A gold-catalyzed formal [4+1] cycloaddition to synthesize substituted 2-aminofurans **464** was developed by Liu's group [186] (Scheme **179**). In the reaction, 3-en-1-ynamides **462** worked as the four-carbon reaction partner and was oxidized by 8-methylquinoline oxide **463** to generate alkenylgold carbenoid **B**, which would undergo an oxa-Nazarov cyclization to furnish the final products.



Scheme 179: Gold-catalyzed formal [4+1] cycloaddition.

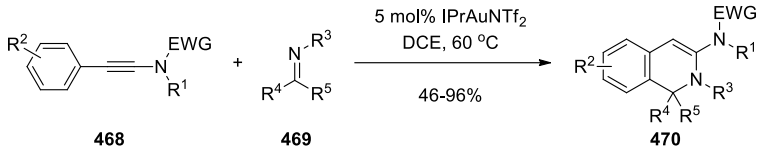
[4+2]

Liu's group [187] demonstrated that 2-aryl-1-ynamides **465** could also serve as the four-carbon reaction partner to react with various electron-rich alkenes **466** by gold catalyst to complete a formal [4+2] cycloaddition (Scheme **180**). It was proposed that the electron-rich alkene would add to the α-position of the Au-activated ynamide to form the cyclopropyl gold carbenoid intermediate **B**, which was then attacked by the tethered phenyl group to furnish the formation of a new 6-membered ring.



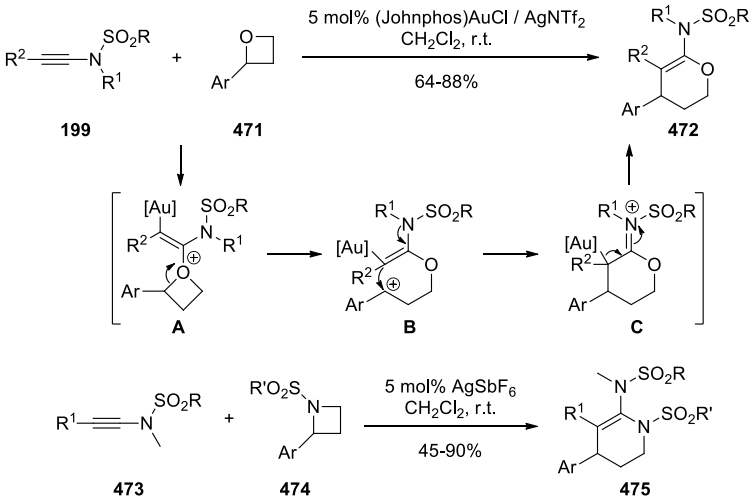
Scheme 180: [4+2] cycloaddition of 2-aryl-1-ynamides and alkenes.

Inspired by Liu's work, Kramer, Skrydstrup, and co-workers [188] successfully used imines **469** to realize a similar gold-catalyzed formal [4+2] cycloaddition with 2-aryl-1-ynamides **468**, providing a new strategy to synthesize 1,2-dihydroisoquinolines **470** (Scheme **181**).



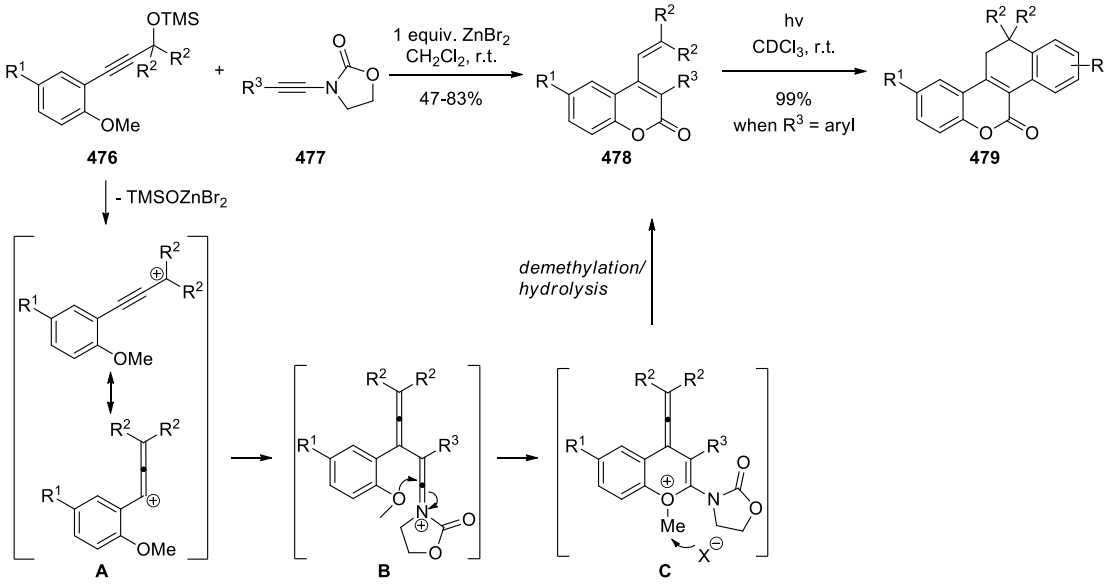
Scheme 181: Synthesis of 1,2-dihydroisoquinolines.

Liu's group [189] further reported a gold-catalyzed [4+2] cycloaddition between oxetanes **471** and ynamides **199** to access 6-membered oxacyclic compounds **472**. During the reaction, alkenyl gold species **A** was proposed to be a key intermediate for the following 4-membered ring opening, which was accelerated by the adjacent aryl group, and a 6-membered ring closure led to the desired oxacycles (Scheme **182**). Azetidines **474** were another kind of 4-membered ring reactant to implement this [4+2] cycloaddition, and $AgSbF_6$ was found to be the most efficient catalyst.



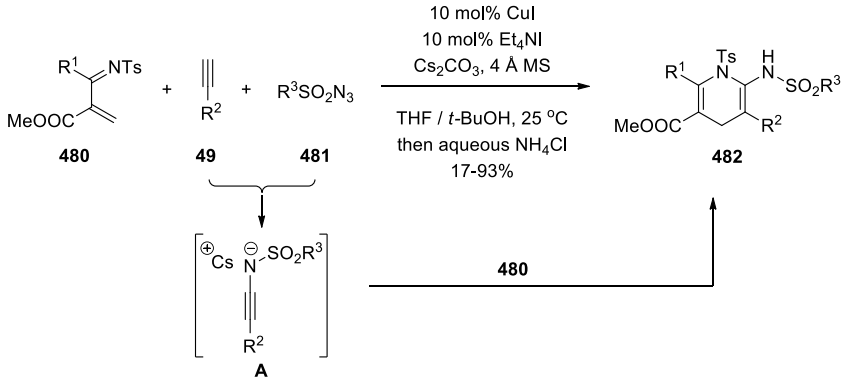
Scheme 182: Cycloadditions of ynamides with oxetanes and azetidines.

Cao, Xu, and co-workers [190] disclosed a carbocation-initiated [4+2] cycloaddition of *o*-anisole-substituted propargyl silyl ethers **476** and ynamides **477** to 4-vinylcoumarins **478** (Scheme **183**). In the presence of stoichiometric amount of $ZnBr_2$, propargyl silyl ethers would be transformed to carbocation **A** with elimination of $TMSO^-$. Subsequent cyclization with ynamide generated intermediate **C**, which was converted into the final product after demethylation and hydrolysis of the oxazolidinone ring. The 4-vinylcoumarins could be further transformed into polycyclic coumarin derivatives **479** *via* electrocyclization by photo-irradiation.



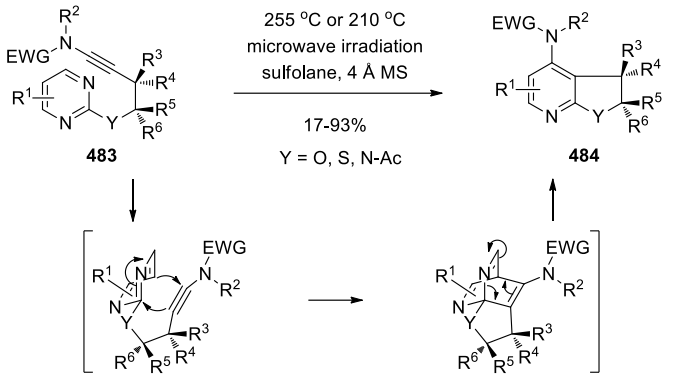
Scheme 183: Synthesis of 4-vinylcoumarins and polycyclic coumarins.

Ma's group [191] developed a three-component reaction of terminal alkynes **49**, sulfonyl azides **481**, and *N*-sulfonyl-1-aza-1,3-butadienes **480** to access functionalized 1,4-dihydropyridines **482** (Scheme **184**). Initial CuI-catalyzed cascade reaction of terminal alkynes and azides with stoichiometric amount of Cs_2CO_3 generated cesium ynamidates **A**, which acted as dienophiles to undergo an inverse hetero-Diels-Alder reaction with azadienes to afford the [4+2] cycloadducts.



Scheme 184: Inverse hetero-Diels-Alder reaction for the synthesis of 1,4-dihydropyridines.

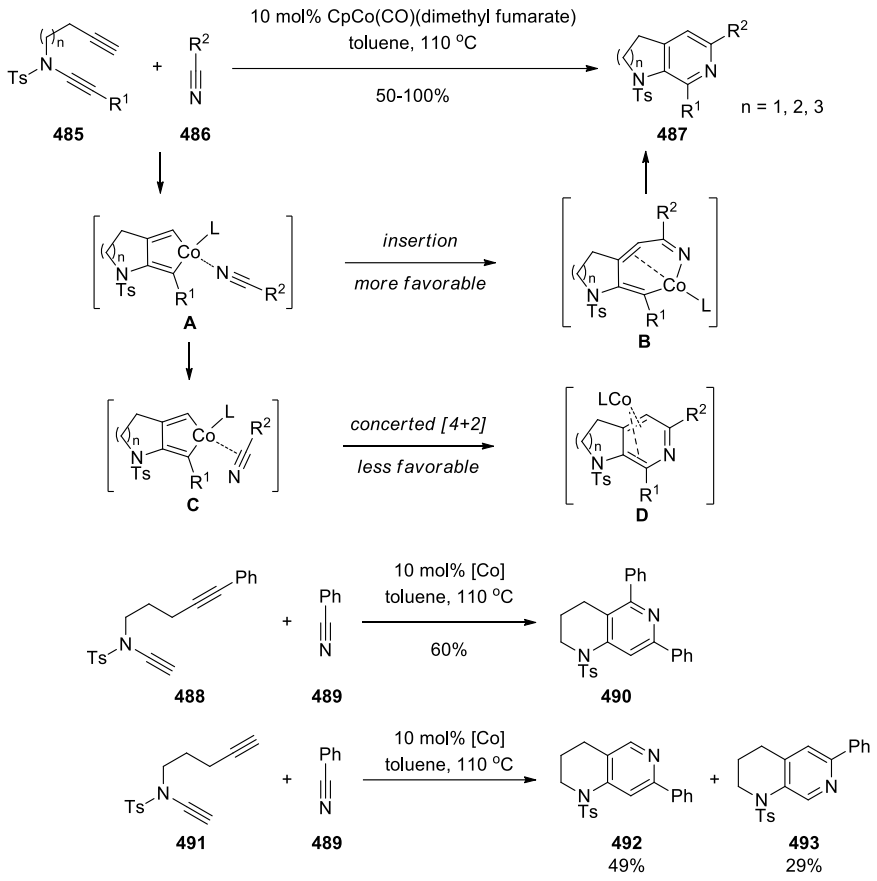
Gandon, Blanchard, co-workers [192] developed an intramolecular inverse hetero-Diels-Alder reaction for the synthesis of 4-aminopyridines **484**, possessing various fused *O*-, *S*-, *N*-containing heterocycles (Scheme **185**). The pyrimidine moiety was selected as electron-deficient heterodiene to react with the ynamide moiety and then sequential retro-Diels-Alder reaction occurred to construct [6-5] pyridines.



Scheme 185: Inverse hetero-Diels-Alder reaction for the synthesis of 4-aminopyridines.

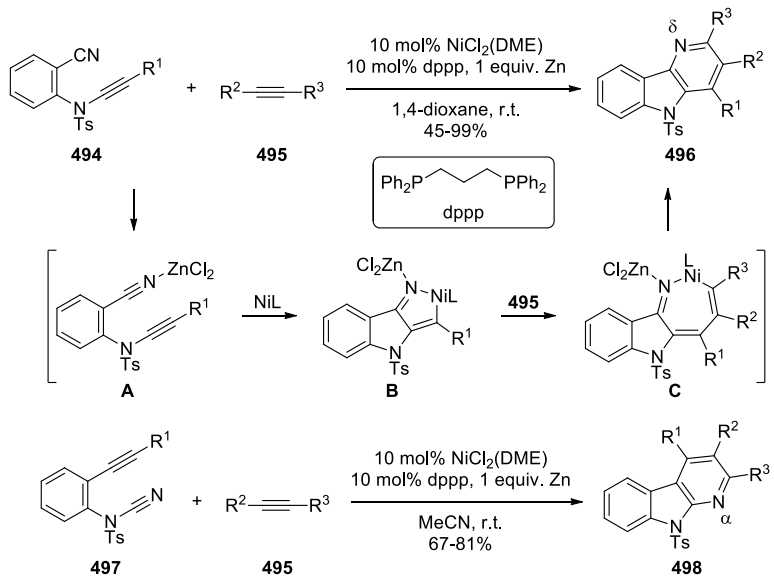
[2+2+2]

Yne-ynamides **485** and nitriles **486** could undergo a Co-catalyzed [2+2+2] cycloaddition to afford bicyclic 3-aminopyridines **487** [193] (Scheme **186**). The cycloisomerization of the yne-ynamide with Co catalyst would generate cobaltacyclopentadiene **A** as the key intermediate in the reaction. The insertion pathway was more favorable for the addition of nitrile to the cobaltacyclopentadiene than the concerted [4+2] pathway according to the calculated reaction barriers [194]. When the substitution pattern of yne-ynamides changed, the regioselectivity of the addition of nitriles would change, resulting in bicyclic 4-aminopyridines **490** and **492** as a major product.



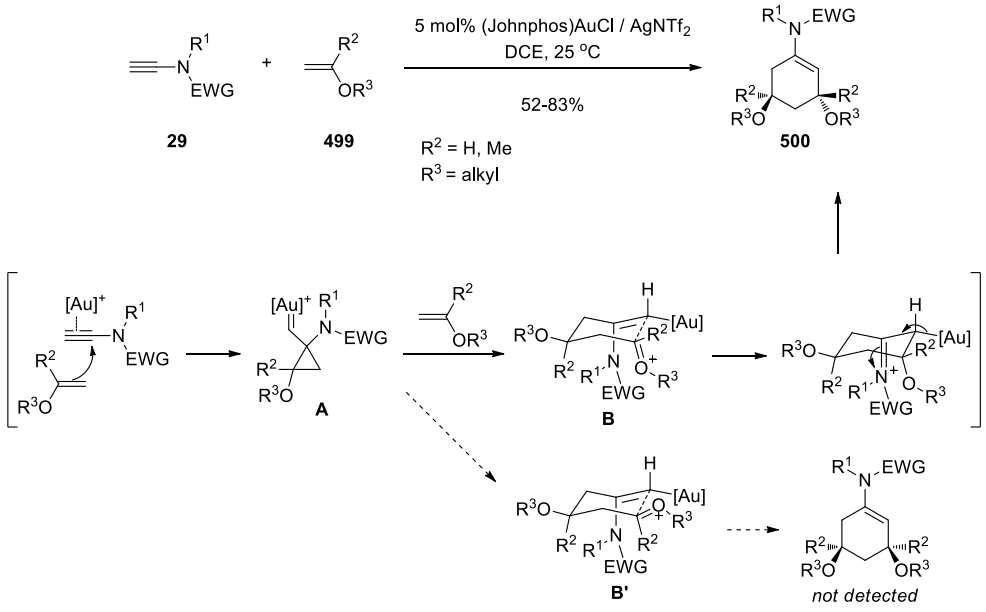
Scheme 186: Synthesis of bicyclic 3- and 4-aminopyridines.

Under the catalytic system of $NiCl_2$(DME) / dppp / Zn, ynamide-nitriles **494** (or alkyne-cyanamides **497**) and alkynes **495** could undergo [2+2+2] cycloaddition to give δ-carbolines **496** or α-carbolines **498** (pyridine-fused indoles), which were of biological interests [195]. The *in-situ* generated $ZnCl_2$ played an important role on increasing the electrophilicity of the nitrile moiety for the successful transformation. Subsequent oxidative addition of the activated ynamide-nitrile to the Ni center led to the azanickelacycle **B**. Insertion of the alkyne to the azanickelacycle **B** followed by reductive elimination delivered the desired product (Scheme **187**).



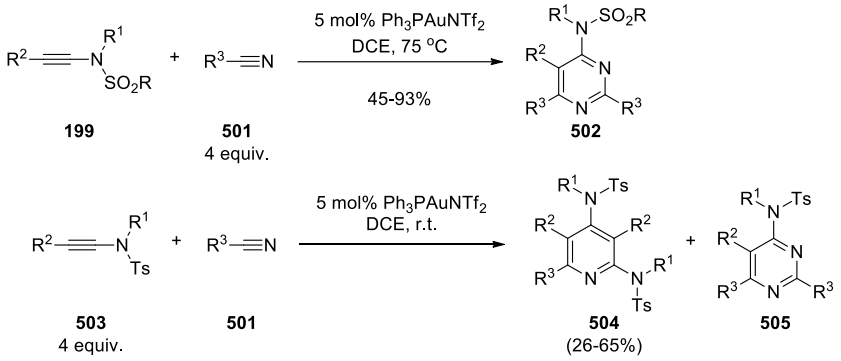
Scheme 187: Synthesis of δ- and α-carbolines.

In the work of gold-catalyzed cycloaddition between 2-aryl-1-ynamides and electron-rich alkenes, Liu's group [186] also reported a [2+2+2] cycloaddition of terminal ynamides **29** with enol ethers **499** to deliver 6-membered carbocycles **500** (Scheme **188**). The authors postulate the enol ether proceeds a nucleophilic addition to the ynamide activated by Au(i), and forms the cyclopropyl gold-carbenoid **A**, followed by a second equivalent of the enol ether addition to give an oxonium species **B** (or **B'**). Conformation **B**, with less 1,3-axial strain between the amino group and the oxonium moiety, leads to the product **500** in a high diastereoselectivity.



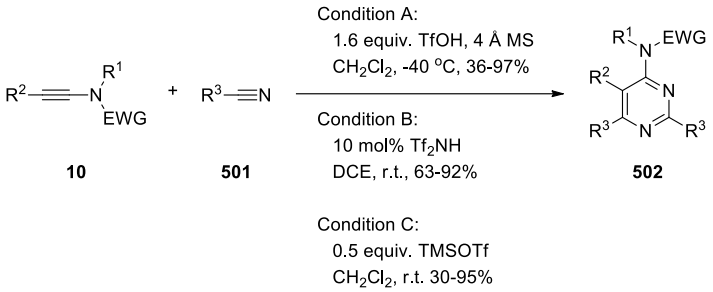
Scheme 188: Cycloaddition of terminal ynamides with enol ethers.

Later, nitriles **501** were introduced to this gold-catalyzed cycloaddition with ynamides **199** [196], which was demonstrated to be an efficient way to construct 4-aminopyrimidine frameworks **502** (Scheme **189**). By increasing the ynamide loading to 4 equivalents with 1 equivalent nitrile, the cycloadduct 2,4-diaminopyridines **504** were formed as the main product from the cycloaddition of two discrete ynamides **503** and one nitrile **501** [197].



Scheme 189: Gold-catalyzed [2+2+2] Cycloadditions of ynamides with nitriles.

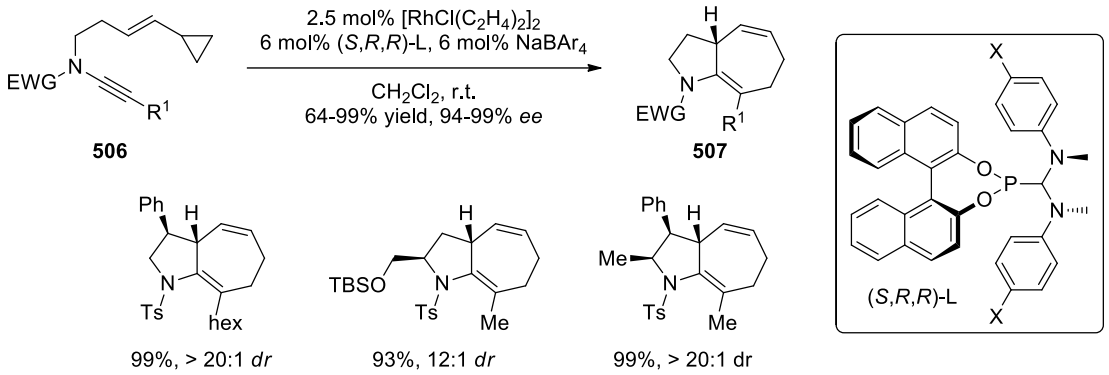
Further studies showed that the [2+2+2] cycloaddition of ynamides and nitriles could also proceed well in the presence of Brønsted acids (*e.g.* TfOH [198], Tf_2NH [199]) and TMSOTf [200] (Scheme **190**).



Scheme 190: Metal-free [2+2+2] Cycloadditions of ynamides with nitriles.

[5+2]

The Anderson's group [201] demonstrated that ynamides **506** featuring a pendant vinylcyclopropane could undergo an intramolecular [5+2] cycloaddition to form [5.3.0]-azabicycles **507**. With the help of computational ligand design, the target products could be obtained in high enantio- and diastereoselectivities as well (Scheme **191**).



Scheme 191: Rhodium-catalyzed [5+2] cycloaddition.

CONCLUSION

The ynamide chemistry has been witnessed to blossom in the past decade with established efficient ways of preparation and unique reactivities. We anticipate that the ynamide chemistry will continue to flourish in the future and the ynamide will turn to be a wider popular synthon in synthesis of alkaloids and diverse molecules that are of biological or pharmaceutical values.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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